

Karyopharm Therapeutics Inc.  
Form 10-K  
March 13, 2015  
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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, 2014**

**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** **(I.R.S. Employer**  
**incorporation or organization)** **Identification No.)**  
**85 Wells Avenue, 2<sup>nd</sup> 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:**

<b>(Title of each class)</b>	<b>(Name of each exchange on which listed)</b>
<b>Common Stock, \$0.0001 par value</b>	<b>NASDAQ Global Select Market</b>
<b>Securities registered pursuant to Section 12(g) of the Act: None</b>	

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, or a smaller reporting company. See definitions of large accelerated filer, accelerated filer, and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer  Accelerated filer

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Non-accelerated filer  (Do not check if a smaller reporting company)  Smaller reporting company   
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, 2014 was approximately \$580,370,783. Shares of common stock held by each executive officer, director, and 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 11, 2015: 35,682,760.

**Documents incorporated by reference:**

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2015 in connection with our 2015 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 our expectations with respect to the possible achievement of discovery and development milestones in 2015, our future discovery and development efforts, our potential 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 we may have in the future, 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 targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on the understanding of the regulation of intracellular transport between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **Selective Inhibitor of Nuclear Export**, or **SINE**, compounds that inhibit the nuclear export protein 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. To our knowledge, no other XPO1 inhibitors are in clinical development at the present time.

Our initial focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as a single orally administered 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 further towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. To date, we have initiated three registration-directed trials in hematological cancers with selinexor, and anticipate initiating a fourth registration-directed trial in the first half of 2015. We intend to establish a commercial infrastructure to prepare for a potential launch of selinexor for hematologic indications in North America and Western Europe, which we expect may occur as early as the second half of 2017 assuming successful results of ongoing clinical trials and receipt of the necessary approvals from regulatory authorities to begin marketing selinexor in these

geographies.

Selinexor is being evaluated in multiple open-label Phase 1 and Phase 2 clinical trials in patients with heavily pretreated relapsed and/or refractory hematological and solid tumor malignancies. To date, we have administered selinexor to over 600 patients across Phase 1 and Phase 2 clinical trials in hematologic and solid tumor indications, including over 450 patients that have been dosed at above 35mg/m<sup>2</sup> (60mg flat dose), which is

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roughly equivalent to Phase 2 or Phase 3 recommended dosing. Evidence of anti-cancer activity has been observed in significant numbers of patients and selinexor has been sufficiently well-tolerated to allow many of these patients to remain on therapy for prolonged periods. Several patients have remained on study for over 12 months, with the longest patient on study for over 24 months. During 2014, we initiated three registration-directed clinical trials of selinexor in three different hematological malignancy indications: older patients with relapsed or refractory acute myeloid leukemia, or AML; Richter's transformation (also called Richter's syndrome), or Richter's, following chemotherapy; and diffuse large B-cell lymphoma, or DLBCL, in third-line or later therapy. We plan to initiate the first cohort in a single-arm trial in multiple myeloma, or MM, in the first half of 2015 that, with an additional cohort, could serve as a registration-directed study. We are evaluating other potential registration-directed trials in hematological and solid tumor indications. These registration-directed trials are designed to serve as the basis for an application seeking regulatory approval for selinexor in particular indications.

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

One of the ways in which a cell regulates the function of a particular protein is by controlling the protein's location within the cell, as a specific function may only occur within a particular location in the cell. In healthy cells, nuclear transport, both into and out of the nucleus, is a normal and regular occurrence that is tightly regulated and requires specific carrier proteins to be present. XPO1 mediates the export of approximately 220 different mammalian cargo proteins, including the vast majority of tumor suppressor proteins, as well as the transport of oncogenic mRNAs which, when transported into the cytoplasm, are translated into functional proteins at high levels. Moreover, XPO1 appears to be the only nuclear exporter for the majority of these tumor suppressor 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 promote programmed cell death, or apoptosis, XPO1 overexpression in cancer cells counteracts the natural apoptotic process that protects the body from cancer. Due to XPO1 inhibition by our SINE compounds, the export of tumor suppressor proteins is prevented, thereby leading to their accumulation in the nucleus. This subsequently reinitiates and amplifies their natural apoptotic function in cancer cells with minimal effects on normal cells. Further, SINE compounds reduce the translation of oncogenes by inhibiting the XPO1-mediated transport of oncogene mRNAs to the cytoplasm. The figure below depicts the process by which our SINE compounds inhibit the XPO1 nuclear export of tumor suppressor proteins.

We believe that the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide a novel, oral, targeted therapy that enables tumor suppressor proteins to remain in the nucleus and promote the apoptosis of potentially any type of cancer cell. Moreover, our SINE compounds spare normal cells, which, unlike cancer cells, do not have significant damage to their genetic



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material, and we believe this selectivity for cancer cells minimizes side effects. We believe that the oral administration of selinexor and the lack of cumulative or major organ toxicities observed to date in patients treated with selinexor in clinical trials create the potential for selinexor's broad use across many cancer types, including both hematological and solid tumor malignancies. We believe that no currently approved cancer treatments or current clinical-stage cancer drug candidates are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. No other XPO1 inhibitors are reported to be in clinical development based on [clinicaltrials.gov](http://clinicaltrials.gov) listings. We own all intellectual property rights related to the SINE compounds that we are developing and our patent application claiming selinexor as a composition of matter was allowed by the U.S. Patent and Trademark Office in late 2014.

### *Summary of Clinical Progress*

We are currently conducting multiple open-label clinical trials of selinexor, including three registration-directed Phase 2 or Phase 2b clinical trials in hematological indications. We refer to these trials as registration-directed because they are designed to serve as the basis for an application seeking regulatory approval of selinexor. In June 2014, we initiated a registration-directed clinical trial for selinexor in older patients with relapsed or refractory AML. In November 2014, we initiated a registration-directed clinical trial in Richter's following chemotherapy. In December 2014, we initiated a registration-directed clinical trial in DLBCL in third-line or later therapy. We plan to initiate the first cohort of patients a clinical trial in MM during the first half of 2015 that, with an additional cohort of patients, could be registration-directed, and we are evaluating other potential registration-directed trials in hematological and solid tumor indications. We plan to seek regulatory approvals of selinexor in North America and Western Europe in each such indication with respect to which we receive positive results and positive regulatory feedback. We may seek such approvals in other geographies as well.

We have also initiated Phase 2 studies of selinexor in several solid tumor indications, including gynecologic malignancies (ovarian, cervical and uterine cancers), glioblastoma, prostate cancer, and squamous head, neck, esophageal or lung cancers. We expect initial data from these studies during 2015. Approximately 19 investigator-sponsored trials, or ISTs, are currently ongoing and a number of additional combination studies, primarily ISTs, are expected to begin during 2015.

During 2014, we reported data from three Phase 1 clinical trials, the first in patients with various advanced hematological malignancies, the second in patients with various advanced or metastatic solid tumor malignancies and the third, a food effect study, in patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. In these trials, we have observed evidence of anti-cancer activity of selinexor across a spectrum of patients with advanced cancers who had received multiple previous treatments and, despite these treatments, had disease that was progressing at the time of enrollment in our clinical trials. Our hematological malignancy trial consists of eight arms, in which selinexor is administered as a monotherapy in Arms 1-5 and Arm 8, and in combination in Arms 6 and 7. Arm 1 includes patients with certain chronic B-cell malignancies, including non-Hodgkin's lymphoma, or NHL, chronic lymphocytic leukemia, or CLL, MM and Waldenström's Macroglobulinemia, or WM; Arm 2 includes patients with AML; Arm 3 includes patients with T-cell lymphomas; Arm 4 includes patients with chronic myeloid leukemia, or CML; Arm 5 includes patients with acute lymphocytic leukemia, or ALL; Arm 6 includes patients on combination therapy who have MM and are taking 20mg of dexamethasone (so called "low-dose dex") in combination with each twice weekly dose of selinexor and Arm 7 includes patients on combination therapy who have DLBCL and are taking standard doses of rituximab in combination with twice weekly doses of selinexor. Arm 8 is a dose evaluation cohort that includes MM patients whose disease is relapsed or refractory to at least three lines of prior therapy and are treated with selinexor at one of three fixed doses without mandatory glucocorticoids.

Of the patients evaluated in our hematological malignancy trial, we have observed complete responses or remissions, partial responses or remissions, minimal responses or stable disease in a number of these patients, all as determined in accordance with commonly accepted evaluation criteria for the specific indication. Complete or partial responses or stable disease were observed in 73% of evaluable patients with relapsed and/or refractory NHL through December 1, 2014. In patients with relapsed or refractory AML as of May 13, 2014, we have observed complete remissions, partial remissions, morphologic leukemia-free state or stable disease in 49% of such patients, some for longer than three months, and as of December 1, 2014, there had been no material

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changes or adverse trends observed in the evaluable AML patient responses. Among nine evaluable patients with MM treated with selinexor in combination with low-dose (20mg) dexamethasone dosed twice weekly, complete, partial or minor responses were observed in 89% of patients as of December 1, 2014. Of the patients in the solid tumor malignancy trial evaluated as of May 13, 2014, we have observed partial responses or stable disease in 49%, all as determined in accordance with Response Evaluation Criteria In Solid Tumors, or RECIST, and as of December 1, 2014, there had been no material changes or adverse trends observed in the evaluable solid tumor patient responses.

*Summary of Additional Development Activity*

We are developing another SINE compound, verdinexor (KPT-335), which is closely related to selinexor, as an oral treatment for pet dogs with lymphomas. The approval of drugs to treat animals is based on a New Animal Drug Application, or NADA, reviewed by the FDA's Center for Veterinary Medicine, or CVM. The use of verdinexor to treat canine lymphoma has been designated a minor use in accordance with the Minor Use Minor Species, or MUMS, Act, which makes verdinexor eligible for conditional approval similar to accelerated approvals used for submissions of human therapeutics. Two of the four major technical sections of the NADA for verdinexor, Effectiveness and Safety, are complete and may support conditional approval by the CVM and the applicability of the Environmental Impact section has been waived. Thus, CVM has indicated that three of the four major technical sections of the NADA support conditional approval. We may seek a commercial relationship with a marketing collaborator to complete the final major technical section of the NADA, the Chemicals/Manufacturing/Controls section, which covers the commercial-scale manufacturing, or CMC, of verdinexor. We believe that the acceptance of the Effectiveness and Safety sections of the NADA for verdinexor for the treatment of dogs with lymphoma helps confirm the activity and tolerability of our novel SINE compounds for the treatment of cancers.

In addition to cancer, we believe that our SINE compounds have the potential to provide therapeutic benefit in a number of additional indications, including wound healing, viral indications and autoimmune / inflammatory diseases. We have discovered and are developing a pipeline of SINE compounds that have shown evidence of activity in preclinical models of wound healing, viral infection and inflammation. In the first half of 2015, we plan to initiate a Phase 1b clinical trial of topical selinexor in patients with diabetic foot ulcers and we expect to initiate a Phase 1 clinical trial in healthy human volunteers for verdinexor, our lead compound for human viral indications in addition to canine lymphoma, during the middle of 2015. In addition, we hope to file an investigational new drug application, or IND, for our oral PAK4 inhibitor covering Phase 1 clinical trials in heavily pretreated oncology patients during the second half of 2015. We may seek to enter into development, marketing and commercialization collaboration arrangements for selinexor in geographies outside North America and Western Europe and for our other SINE compounds in non-oncology indications globally.

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The table below summarizes the current stages of development of our key human drug candidates and indications that we expect to initially focus on for each candidate. In addition, approximately 19 ISTs for selinexor as single-agent or in combination are currently ongoing. We expect a growing number of ISTs to be initiated for selinexor in a variety of cancer indications over the next year consisting of single agent or combination studies in both hematological and solid tumor malignancies.

**Karyopharm's Broad Therapeutic Pipeline**

\* Designed to serve as the basis for an application seeking regulatory approval for selinexor for the specified indication.

Since our founding by Dr. Sharon Shacham in December 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. 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, prior to her founding of Karyopharm and while at Karyopharm.

Since our inception, we have devoted substantially all of our efforts to research and development, and we have not generated any revenue to date from sales of any drugs. As of December 31, 2014, we had an accumulated deficit of \$138.3 million. We had net losses of \$75.8 million, \$33.9 million and \$15.9 million for the years ended December 31, 2014, 2013 and 2012, 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.

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### **Our Strategy**

As a clinical-stage pharmaceutical company focused on the discovery and development of orally available, novel first-in-class drugs directed against nuclear transport targets for the treatment of cancer and other major diseases, the critical components of our business strategy are to:

***Develop and Seek Regulatory Approval of Selinexor, Our Novel Lead Drug Candidate, in North America and Western Europe.*** We plan to seek regulatory approvals of selinexor in North America and Western Europe in each indication subject to a registration-directed trial with respect to which we receive positive clinical trial results and positive regulatory feedback. We may seek such approvals in other geographies as well. In solid tumor malignancies, we have initiated four Phase 2 studies of selinexor in several solid tumor indications, including gynecologic malignancies (ovarian, cervical and uterine cancers), glioblastoma prostate cancer, and squamous head, neck, esophageal or lung cancers.

***Maximize the Commercial Value of Selinexor.*** We currently have global development, marketing and commercialization rights for selinexor and we expect that we will continue to develop and seek regulatory approval for its use in oncology indications without a collaborator in North America and Western Europe. We intend to enter into collaborations for further development, marketing and commercialization of selinexor in particular geographies outside of North America and Europe at an appropriate time.

***Maintain our Competitive Advantage and Scientific Expertise in the Field of Nuclear Transport.*** We plan to continue to conduct research in the field of nuclear transport to further our understanding of the role it plays in the underlying biology of cancer, as well other major diseases. We also plan to continue fostering relationships with top scientific advisors and physicians. We believe that investing in the recruitment of exceptional advisors, employees and management is critical to our continued leadership in the nuclear transport field.

***Continue to Build a Pipeline of Novel Drug Candidates.*** To date, we have identified selinexor, other SINE compounds, including verdinexor, and a series of PAK4 inhibitors. We plan to continue to identify or in-license novel drug candidates for development in oncology.

***Collaborate with Key Opinion Leaders to Conduct Investigator-Sponsored Trials of Selinexor.*** A significant part of our strategy for continuing to efficiently assess the breadth of activity of selinexor alone or in combination with other anti-cancer drugs includes the initiation of investigator-sponsored trials. We plan to continue to facilitate the investigation of the breadth of the clinical activity of selinexor through our established network of scientific advisors and physicians.

***Maximize the Value of Our Other SINE Compounds in Non-Oncology Indications through Collaborations.*** We may seek to enter into development, marketing and commercialization collaboration arrangements for our other SINE compounds in non-oncology indications globally.

### **Our Focus: Nuclear Transport**

A human cell is divided into various compartments, including the nucleus and the cytoplasm. The nucleus contains a cell's genetic material, or DNA, and is the compartment where gene expression and consequently cellular function is regulated. The cytoplasm is the compartment around the nucleus where translation of gene transcripts, or mRNA, to proteins, assembly of proteins into cellular structural elements, and cellular metabolism of fats, carbohydrates, and proteins, occur. One of the ways in which the cell regulates the function of a particular protein is by controlling the protein's location within the cell, as a specific function may only occur within a particular location. Certain proteins, including tumor suppressor proteins and other growth regulatory proteins, need to be transported from the cytoplasm, where they are made, into the nucleus where they need to be located for their primary functions to occur. The nuclear pore is a complex gate between the nucleus and cytoplasm, closely 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 processes of macromolecules in either direction through the nuclear pore are tightly regulated and require specific carrier proteins, including nuclear export proteins, to occur. There are eight known nuclear export proteins. The most well-characterized was discovered in 1999 and is called Exportin 1, or XPO1 (also called CRM1). XPO1 mediates the export of

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approximately 220 different mammalian cargo proteins, including some growth regulatory proteins and the vast majority of tumor suppressor proteins. Moreover, XPO1 appears to be the only nuclear exporter for the majority of these tumor suppressor proteins, including those generally referred to as p53, p73, FOXO, pRB, BRCA1, BRCA2, NPM1, IκB and PP2A.

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when DNA in normal cells begins to accumulate mutations or other abnormalities, causing genes that regulate cell growth become disrupted. Tumor suppressor proteins are an integral part of the body's natural defense mechanism in identifying and preventing cancer. When DNA damage is detected, tumor suppressor proteins promote apoptosis. Tumor suppressor proteins can also have an anti-cancer effect by dampening unregulated cell growth and division. In addition to tumor suppressor proteins, cells contain growth regulatory proteins that, when located in the nucleus, are involved in ensuring that cells undergo cell division, or cell growth, only under appropriate circumstances, such as repairing wounds, increasing cell numbers to deal with damage to an organ, or replacing cells that have died through normal circumstances. Growth regulatory proteins are also exported from the nucleus by XPO1 in all cells. Examples of well-characterized growth regulatory proteins are p21, p27 and E2F4.

In addition to transporting tumor suppressor proteins, XPO1 is the sole transporter of the eukaryotic initiation factor 4E (eIF4E) protein, also called the mRNA cap binding protein. eIF4E carries the mRNAs for many growth promoting proteins, including certain oncoproteins such as c-myc, Bcl2, hDM2 and cyclin D from the nucleus into the cytoplasm (dependent on XPO1) followed by association with ribosomes for translation into proteins. Blockade of XPO1 leads to accumulation of eIF4E in the cell nucleus and concomitant nuclear trapping of bound oncoprotein mRNAs, leading to reduced translation of the mRNAs, and reductions in oncoprotein levels.

XPO1 is also the only exporter of the anti-inflammatory protein IκB, the inhibitor of NF-κB. NF-κB is known to play a role in cancer metastasis and resistance to chemotherapy as well as in many inflammatory and autoimmune diseases. Blockade of XPO1 leads to accumulation of IκB in the cell nucleus where it binds to and inhibits NF-κB. In this way, the inhibition of NF-κB may be beneficial in overcoming chemotherapy resistance and in treating autoimmune diseases.

Because tumor suppressor proteins need to be located in the nucleus in order to carry out their anti-cancer activities, their nuclear export, or exit from the nucleus, leads to their being unavailable in the nucleus to identify cancer cells and initiate their death. As XPO1 levels have been shown to be elevated by two- to four-fold in nearly all cancer cells compared to their normal cell counterparts, it appears that cancer cells have co-opted XPO1 to move tumor suppressor proteins out of the nucleus, thereby adversely affecting their ability to identify and initiate the death of cancer cells. Increased levels of XPO1 in cancer cells also lead to excessive nuclear export of growth regulatory proteins as well as oncoprotein mRNAs. All of these XPO1 effects allow cancer cells to divide continuously and inappropriately. Higher levels of XPO1 expression are also generally correlated with poor prognosis and/or resistance to chemotherapies. The figure below depicts the process by which XPO1 mediates the nuclear transport process.

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**XPO1 Mediation of Nuclear Transport**

**Our Approach: Targeting Nuclear Export with SINE Compounds**

Since the discovery of XPO1, a growing body of research has documented that the high levels of XPO1 found in cancer cells are associated with the transport of tumor suppressor proteins and growth regulatory proteins from their site of action in the nucleus into the cytoplasm, where their anti-cancer activity is minimal and they are ultimately degraded. The inhibition of XPO1 cargo binding has been studied for over ten years. XPO1 inhibitors block the nuclear export of tumor suppressor proteins and growth regulatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. The forced nuclear retention of these proteins can counteract a multitude of the oncogenic pathways that allow cancer cells with severe DNA damage to continue to grow and divide in an unrestrained fashion. XPO1 inhibitors also force the nuclear retention of eIF4E and its cargo oncoproteins mRNAs, preventing their transport to the cytoplasm for ribosomal translation, leading to reduced levels of oncoproteins. One naturally occurring XPO1 inhibitor called leptomycin B has been shown to have potent anti-cancer activity *in vitro*, but has been toxic to normal cells. These toxicities to normal cells have been observed in both animals and humans, which we believe are most likely caused by the *irreversible* nature of leptomycin B binding to XPO1. Because of its observed toxicities in animals and humans, to our knowledge, leptomycin B is no longer being developed.

Our lead drug candidates are first-in-class, oral **Selective Inhibitor of Nuclear Export**, or **SINE**, compounds. We have discovered SINE compounds by applying our proprietary drug discovery and optimization expertise to the published X-ray structure of XPO1. SINE compounds inhibit XPO1-mediated nuclear-cytoplasmic transport by *transiently* binding to the XPO1 cargo binding site, meaning that they block XPO1 cargo binding over an extended period of time, but do not permanently do so. Transient XPO1 inhibition, or inhibition for approximately 12 to 24 hours, which corresponds to the inhibition period that we have observed to date with our SINE compounds, appears to be sufficient for nuclear retention and elevation of tumor suppressor protein levels in the nucleus. During this period, the inhibition of XPO1 cargo binding enables tumor suppressor proteins to accumulate in the nucleus of cancer cells and perform their normal role of detecting DNA damage, thereby inhibiting a cancer cell's ability to divide and promoting apoptosis. Healthy cells also build up tumor suppressor proteins in the presence of a SINE compound, but are able to resume normal activity after transient XPO1 inhibition because they have an intact genome with minimal or no DNA damage. The figure below depicts the process by which SINE compounds inhibit the XPO1 nuclear export of tumor suppressor proteins.



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**Transient XPO1 Inhibition by SINE Compounds**

We believe that the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide a novel targeted therapy that enable tumor suppressor proteins to remain in the nucleus and promote apoptosis of cancer cells. Moreover, 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. We believe that the oral administration of selinexor and the lack of cumulative or major organ toxicities observed to date in patients treated with selinexor in our Phase 1 and Phase 2 clinical trials create the potential for its broad use across many cancer types, including both hematological and solid tumor malignancies. We believe that no currently approved cancer treatments or current clinical-stage cancer drug candidates are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus.

In addition to cancer, we believe that our SINE compounds have the potential to provide therapeutic benefit in a number of additional indications, including wound healing, viral indications and autoimmune / inflammatory diseases. We have discovered and are developing a pipeline of SINE compounds that have shown evidence of activity in preclinical models of inflammation, wound healing and viral infection. Specifically, our SINE compounds have shown potent evidence of anti-inflammatory activity in several animal models of inflammation, including systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis. Our SINE compounds have also shown evidence of activity as topical formulations in wound healing by accelerating wound closure and improving wound appearance in both mouse and pig models of surgical and/or knife wounds. In addition, in preclinical studies, our SINE compounds have shown evidence of activity against specific viruses which require XPO1 for their replication, including HIV and influenza.

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### **Our Initial Indication: Cancer**

Cancer is a leading cause of death worldwide, with approximately 8.2 million cancer deaths globally in 2012, according to the American Cancer Society. In the United States, the American Cancer Society estimates that in 2015, approximately 590,000 people will die of cancer and approximately 1.7 million new cancer cases will be diagnosed. The International Agency for Research on Cancer projects that in 2030, 21.4 million people will be diagnosed with cancer, and 13.2 million people will die of cancer worldwide, as compared to 12.7 million new cancer diagnoses and 7.6 million cancer deaths worldwide in 2008.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. In many cases, drug therapy entails the administration of several different drugs in combination. An early approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific 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 rapid cell growth and the spread of cancer. Targeted therapeutics are designed to specifically enable the death of cancer cells and spare normal 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 either a specific genetic alteration primarily found in cancer cells, but not in normal cells, or a target that cancer cells are more dependent on for their growth in comparison to normal cells.

Our SINE approach is a novel targeted therapeutic approach specifically focused on selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins and growth regulatory proteins in the nucleus. Unlike many other targeted therapeutic approaches which only work for a specific set of cancers or in a specific sub-group of patients, we believe that our SINE compounds have the potential to provide therapeutic benefits across a broad range of both hematological and solid tumor malignancies and benefit a wide range of patients.

### **Our Drug Candidates**

#### ***Selinexor (KPT-330)***

Selinexor is being evaluated in multiple open-label Phase 1 and Phase 2 clinical trials in patients with heavily pretreated relapsed and/or refractory hematological and solid tumor malignancies. During 2014, we reported updated data from our ongoing Phase 1 clinical trials of selinexor in patients with various advanced hematological malignancies and in patients with various advanced or metastatic solid tumor malignancies. All patients entering these trials have progressive disease upon enrollment that is relapsed after and/or refractory to all available classes of anti-cancer agents, typically after multiple approved therapies and often after one or more experimental therapies. To date, we have administered selinexor to over 600 patients across Phase 1 and Phase 2 clinical trials in hematologic and solid tumor indications, including over 450 patients that have been dosed at above 35mg/m<sup>2</sup> (60mg flat dose), which is roughly equivalent to Phase 2 or Phase 3 recommended dosing. Anti-cancer activity has been observed with tumor reductions and durable disease control across many hematologic and solid tumor malignancies. Several patients have remained on single-agent oral selinexor for over 12 months with the longest on therapy for over 24 months. Adverse

events observed in our most recent patient data are generally mild, responsive to standard supportive care and consistent with those previously reported in patients in our Phase 1 clinical trials.

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Response data presented herein are interim unaudited data based on reports by physicians at the clinical trial sites. Responses in the hematological trial are measured using commonly accepted evaluation criteria for the specific indication. Responses in the solid tumor trial are measured using RECIST. Responses include:

sCR stringent complete response;

CR complete response;

CR(i/p) complete response without hematological recovery;

PR partial response;

MLFS morphological leukemia free state;

MR minimal response;

SD stable disease;

PD progressive disease;

WC withdrew consent; or

NE non-evaluable, meaning the patient's response could not be evaluated due to a number of potential factors, including when a patient withdraws consent or fails to comply with the therapeutic protocol for the trial.

Disease control rate, or DCR, refers to the percentage of responses that are SD or better (MR or better in the case of MM) and overall response rate, or ORR, refers to the percentage of responses that are PR or better.

*Advanced Hematological Malignancies*

During December 2014, we reported data from patients with NHL, including DLBCL, Richter's, AML and MM, as part of our ongoing Phase 1 clinical trial of selinexor in patients with various advanced hematological malignancies. The primary objectives of the Phase 1 trial are to determine the safety, tolerability and recommended Phase 2 and Phase 3 dose of orally administered selinexor. Patients were dosed 3-80mg/m<sup>2</sup> (equivalent to approximately 5-130mg) of selinexor orally over a four-week cycle, with lower doses initially given ten times per cycle and higher doses usually given twice weekly. Responses were evaluated every one to two cycles.

**Acute Myeloid Leukemia**

AML in elderly populations remains a vexing clinical problem. 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 21,000 new cases of AML, most of which will be in adults, will be diagnosed in the United States in 2015, with approximately 10,000 deaths from AML in the United States in 2015. 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. 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.

Over the past two decades, many compounds have been evaluated in elderly patients with AML, but due to significant toxicities and/or lack of efficacy, none has been approved to date. Adults who are not transplant candidates, and cannot safely receive intensive chemotherapy, like anthracyclines and cytosine arabinoside, or AraC, are usually treated with best supportive care, or BSC, including blood transfusions, antibiotics and hydroxyurea if indicated, along with hypomethylating agents decitabine (Dacogen<sup>®</sup>) or azacytidine (Vidaza<sup>®</sup>). Some patients are treated with low dose AraC. All of these agents are given parenterally (subcutaneously or intravenously) in the clinic or hospital, and none of these agents are associated with cures, meaning that all older patients unfit for chemotherapy will relapse and eventually succumb to their disease. Median survival following initial treatment with front-line therapy in these patients is reported to be less than three months.

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In June 2014, we dosed the first patient in our registration-directed Phase 2 study of selinexor in patients 60 years of age or older with relapsed or refractory AML who are ineligible for standard intensive chemotherapy and/or transplantation. In this trial, known as SOPRA, or Selinexor in Older Patient with Relapsed/Refractory AML (NCT 02088541), we are evaluating approximately 150 patients with AML which has relapsed after, or was refractory to, first line therapy. Patients are randomized in a 2:1 fashion to selinexor provided orally twice weekly in a dose of 55mg/m<sup>2</sup> plus BSC versus one of three physician choices. Physician choices include (i) BSC alone, (ii) BSC plus either azacytidine (Vidaza<sup>®</sup>) or decitabine (Dacogen<sup>®</sup>), or (iii) BSC plus low dose AraC. Overall survival is the primary endpoint. The SOPRA study was designed based on data from the ongoing Phase 1 study of selinexor in patients with advanced hematologic malignancies, including AML. The SOPRA study is expected to take approximately two years from initiation to report top-line data.

We enrolled 65 heavily pretreated patients with progressive, relapsed and/or refractory AML, most with three or more prior treatment regimens, in our Phase 1 clinical trial in hematological malignancies as of May 13, 2014. These patients were dosed 16.8-70mg/m<sup>2</sup> of selinexor in a four-week cycle, with lower doses initially given ten times per cycle and higher doses given twice weekly. Of these 65 patients, two patients had tumors pending evaluation, and among the 63 other patients, the complete response rate with or without full hematologic recovery was 11%, the ORR was 16% and the DCR was 49%; 16 (25%) of the 63 patients with AML were non-evaluable but were included in the AML response rate calculation. Responses were observed across multiple genetic subtypes of AML. Higher doses of selinexor were associated with greater reductions in bone marrow blast counts, which were also observed across different AML subtypes. Responses in 63 patients, 47 of whom were evaluable, are shown below. As of December 1, 2014, there had been no material changes or adverse trends observed in the evaluable AML patient responses.

**Best Responses in AML Patients as of May 13, 2014**

N	DCR (%)	ORR (%)	CR (%)	CR(i/p) (%)	PR (%)	MLFS (%)	SD (%)	PD (%)	NE (%)
63	31 (49%)	10 (16%)	5 (8%)	2 (3%)	1 (2%)	2 (3%)	21 (33%)	16 (25%)	16 (25%)

Grade 3/4 adverse events occurring in more than three patients included fatigue (18%), thrombocytopenia (15%), neutropenia (11%), and nausea (8%). The most common Grade 1/2 adverse events were diarrhea (82%), anorexia (78%), nausea (74%), and fatigue (65%). There have been no dose limiting toxicities in AML patients as of May 13, 2014 and the maximum tolerated dose is 70mg/m<sup>2</sup> twice weekly. The intended Phase 2 or Phase 3 trial dose of oral selinexor for AML is 60-80mg twice weekly.

**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. The World Health Organization estimated that 386,000 new cases of NHL would be diagnosed worldwide in 2012 and the American Cancer Society projects that approximately 72,000 patients will be diagnosed with NHL in the United States in 2015.

We have initiated two registration-directed trials of selinexor in NHL indications, one in DLBCL and the other in Richter s.

*Diffuse Large B-cell Lymphoma*

DLBCL is the most common of the aggressive NHLs. We estimate that approximately 25,000 patients are diagnosed with DLBCL in the United States each year, with approximately 10,000 deaths per year.

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The fundamental treatment of DLBCL has changed little in the past two decades, with no new or targeted agents approved for this indication. Initial therapy with multiagent, or three to four, cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan<sup>®</sup>) leads to cures in approximately 50% of patients. Patients who are not cured with initial immune-chemotherapy have a poor prognosis. Of the approximately 30% of patients who are less than 65 years old and have good organ function, high dose chemotherapy with stem cell transplantation can lead to cures in approximately half. Older patients relapsing after initial chemotherapy, and those relapsing after stem cell transplantation, have a very poor prognosis, and the expected survival of such patients is less than one year. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica<sup>®</sup>) and the immunomodulatory drug lenalidomide (Revlimid<sup>®</sup>) have shown activity in the immunoblastic (activated B-cell or ABC) type of DLBCL in clinical trials, but responses are generally short-lived. Responses to these newer agents are much lower in the germinal center, or GCB, type of DLBCL. Therefore, with 10,000 deaths in United States each year due to DLBCL, we believe that novel, well-tolerated drugs are needed for the treatment of relapsed/refractory DLBCL.

The first patient in our registration-directed trial in DLBCL, a Phase 2b clinical trial known as the SADAL, or Selinexor Against Diffuse Aggressive Lymphoma, study (NCT 02227251), was dosed in December 2014. This is a two-arm open-label trial in patients that have relapsed and/or refractory de novo DLBCL after at two to four lines of therapy. The primary endpoint of this trial is ORR and duration of response, or DOR. There are two arms in the study: 100mg versus 60mg of selinexor, with about 200 patients randomized evenly between the two arms. Patients will also receive supportive care in accordance with applicable treatment guidelines and the discretion of the treating physician. The SADAL study is expected to take approximately two years from initiation to top-line data.

*Richter's Transformation*

Richter's describes the transformation from CLL to a type of NHL that is similar to DLBCL and is characterized by a distinct worsening of symptoms. The American Cancer Society estimates that 14,620 patients will be diagnosed with CLL in the United States in 2015, and that over 100,000 suffer from the disease. According to the largest published study on Richter's transformation conducted by researchers at MD Anderson Cancer Center, 8.8% of patients with CLL will experience Richter's transformation. Therefore, we estimate that approximately 1,200 patients will develop Richter's transformation in the United States in 2015. Although there are no specific therapies approved to treat Richter's, multi-agent chemoimmunotherapy is typically used as a first line treatment, but overall survival is typically less than one year from diagnosis.

The first patient in our registration-directed trial in Richter's, a Phase 2 clinical trial known as the Selinexor In Relapsed/Refractory Richter's Transformation, or SIRRT, study (NCT 02138786), was dosed in November 2014. This is a single-arm open-label trial in patients with CLL who experienced Richter's and subsequently relapsed after chemotherapy. The primary endpoints of this trial are ORR and duration of response, or DOR. Patients will be treated with selinexor given at a dose of 60mg, administered orally two times per week in weeks one through three of each four-week cycle, until disease progression or intolerability. The SIRRT study is expected to take approximately two years from initiation to top-line data.

*Phase 1 Clinical Trial Data in Non-Hodgkin's Lymphoma*

In our Phase 1 trial, as of December 1, 2014, 71 heavily pretreated patients with relapsed and/or refractory NHL, including DLBCL and Richter's, and median prior treatment regimens of three were enrolled in this arm of this clinical trial. Of this group, as of December 1, 2014, 52 patients were evaluable for response. The DCR was 73% across all doses of selinexor and the ORR was 37%. Responses were observed across all subtypes of NHL, independent of genetic abnormalities, with durable cancer control observed across several patients who remained on study for longer than nine months, with the longest for 24 months. The median DOR in patients was





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approximately seven months as of December 1, 2014. Responses in these 52 evaluable patients are summarized below.

**Best Responses in NHL Patients as of December 1, 2014**

Type	N	DCR (%)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
DLBCL	32	21 (66%)	11 (34%)	4 (13%)	7 (22%)	10 (31%)	11 (34%)
Richter s	4	4 (100%)	2 (50%)		2 (50%)	2 (50%)	
Other NHL	16	13 (81%)	6 (38%)	1 (6%)	5 (31%)	7 (44%)	3 (19%)
Total	52	38 (73%)	19 (37%)	5 (10%)	14 (27%)	19 (37%)	14 (27%)

Among the 32 patients with heavily pretreated DLBCL who were evaluable as of December 1, 2014, ORR and DCR were nearly identical across all subtypes of DLBCL. There are two major subtypes of DLBCL, namely Germinal-Center B-Cell (GCB) and Activated B-Cell (ABC), also called non-GCB. Many targeted therapies such as ibrutinib or lenalidomide show activity primarily against the ABC subtype (although all patients relapse), but there are no viable treatment options for patients with relapsed/refractory GCB. However, as detailed in the table below and consistent with the broadly applicable mechanism of action of selinexor, selinexor shows activity across both major subtypes.

**Best Responses in Diffuse Large B-Cell Patients as of December 1, 2014**

Type	N	DCR (%)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
GCB	11	9 (82%)	4 (36%)	1 (9%)	3 (27%)	5 (45%)	2 (18%)
non-GCB	5	4 (80%)	2 (40%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)
Unknown	16	8 (50%)	5 (31%)	2 (13%)	3 (19%)	3 (19%)	8 (50%)
Total	32	21 (66%)	11 (34%)	4 (13%)	7 (22%)	10 (31%)	11 (34%)

In addition, a minority of DLBCL patients have double-hit disease because these tumors over-express the two oncogenes MYC and BCL2 (or BCL6). Double-hit DLBCL is particularly difficult to treat due in part to its resistance to multi-agent immunochemotherapy and many targeted agents; essentially all patients with double-hit DLBCL will relapse after initial therapy, or have tumors that fail to respond (i.e., are refractory) to initial and subsequent therapies. Of four patients with double-hit DLBCL as of December 1, 2014, there was one patient with a CR (on study 440 days and remained on study as of December 1, 2014), one patient with a PR (on study 214 days), one patient with SD (45% lymph node reduction on study 104 days) and one patient with PD (on study 57 days). We believe that these data and the consistent data across DLBCL subtypes indicate that selinexor has the potential to treat a broad range of subtypes of DLBCL, largely independent of the cell of origin or oncogenic drivers.

Among all NHL patients, Grade 3/4 adverse events occurring in more than three patients out of 67 included thrombocytopenia (39%), neutropenia (24%), hyponatremia (10%), fatigue (12%) and dehydration (6%). The most common Grade 1/2 adverse events were nausea (64%), anorexia (52%), fatigue (46%), vomiting (36%) and diarrhea (23%). There has been one case of dose limiting toxicities among NHL patients as of December 1, 2014, grade 4 thrombocytopenia lasting over seven days without bleeding. The maximum tolerated dose was not reached, but based on biological activity and data from additional studies, the recommended Phase 2 or Phase 3 trial dose of oral selinexor for NHL is 60-100mg twice weekly.

## **Multiple Myeloma**

MM is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, or 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 27,000 new cases of MM, with about 11,000 attributable deaths, in 2015. Approximately 114,000 cases are expected worldwide each year.

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The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, the subsequent introduction of the immunomodulatory agents such as lenalidomide (Revlimid®) and pomalidomide (Pomalyst®) and the proteasome inhibitors bortezomib (Velcade®) and carfilzomib (Kyprolis®). The median overall survival of MM patients, meaning the length of time an MM patient survives with the disease, has increased significantly in patients younger than 50 years old, with those patients experiencing a 10-year survival rate of around 40%, meaning that 40% of those patients are still alive after 10 years. Although a wide variety of new agents are being used in relapsed and/or refractory patients, including new proteasome inhibitors (ixazomib, oprozomib and marizomib), monoclonal antibodies (elotuzumab and daratumumab), histone deacetylase inhibitors (panobinostat (Farydak®)), nearly all patients will eventually relapse and their disease will become drug-resistant. With over 22,000 deaths from MM in the United States and Europe expected in 2015, we believe that there remains a need for therapies in these relapsed and/or refractory patients that can improve the overall survival rate.

Based on ongoing discussions with regulatory authorities and key opinion leaders regarding trial design, we intend to initiate a Phase 2 clinical trial for selinexor combined with low dose dexamethasone (low-dose dex) in patients with heavily pretreated MM during the first half of 2015. In the **S**elinexor **T**reatment **O**f **R**efractory **M**yeloma, or STORM, study, we expect to treat patients with quadruple refractory MM, meaning MM that has been treated with and is refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide. We expect that patients will also have to have received prior alkylating agents (such as melphalan and/or cyclophosphamide) and glucocorticoids (such as dexamethasone) and some patients will also have received anti-CD38 monoclonal antibodies. If the results in the first cohort of approximately 80 patients from this trial appear promising, we expect to increase the size of this study and intend for these two cohorts of patients to be able to serve as the basis for an application seeking regulatory approval. We expect that the primary endpoint will be ORR and ORR compared to a minimally effective lower threshold of ORR (15%) and that the trial will have several secondary endpoints, including ORR in patients whose disease is relapsed/refractory to an anti-CD38 monoclonal antibody and DOR. Once initiated, this trial is expected to take approximately two and a half years (15 months for each of the two cohorts) to complete.

A second combination study evaluating selinexor in MM patients is ongoing. This Phase 1/2 investigator-sponsored clinical trial is being conducted at the University of Chicago to evaluate tolerability and efficacy of the combination of selinexor with carfilzomib and low-dose dexamethasone. As of December 1, 2014, the best responses in the first three treated patients, all of whom have MM that is refractory to carfilzomib and dexamethasone in their most recent therapy, were one very good partial response, or VGPR, and two PRs, with good tolerability in each case. The primary objectives of the study are to determine the maximum tolerated dose and recommended Phase 2 and Phase 3 doses for selinexor in these combination therapies in the dose-escalation phase and to assess preliminary efficacy through ORR, clinical benefit rate, or CBR, and DOR in the expansion phase. The dose escalation phase in this clinical study is ongoing.

In addition to the ongoing investigator-sponsored trial of selinexor in combination with carfilzomib and dexamethasone, we intend to initiate a combination trial, which would be a company-sponsored Phase 1b/2 clinical trial for selinexor in combination with approved therapies to treat MM, during the middle of 2015. This two arm trial will evaluate selinexor in combination with dexamethasone and pomalidomide, or the SdP Arm, and selinexor in combination with dexamethasone and bortezomib, or the SdB Arm. The SdP Arm will accrue patients who received at least two prior therapies, including lenalidomide, a proteasome inhibitor, and glucocorticoids, with progression during or within 60 days of completion of last therapy (i.e., patients whose disease is refractory to their most recent therapy). The SdB Arm will accrue patients whose disease is relapsing after at least one line of therapy, and whose disease is not refractory to bortezomib in their most recent line of therapy. The primary objectives of the study are to determine the maximum tolerated dose and recommended Phase 2 and Phase 3 doses for selinexor in these combination therapies and to assess preliminary efficacy through ORR, CBR and DOR. We expect to determine the recommended Phase 2 and Phase 3 trial doses for selinexor in these combinations by the end of 2015 and the trial is expected to be

complete by the end of 2016.

As part of our Phase 1 clinical trial of selinexor in patients with advanced hematological malignancies, patients with MM were treated with either single-agent selinexor or selinexor in combination with low-dose

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(20mg) dexamethasone, all dosed twice weekly. As of December 1, 2014, nine evaluable patients were treated with 45mg/m<sup>2</sup> of oral selinexor and 20mg of dexamethasone, each dosed twice weekly. This dose of selinexor, equivalent to approximately 80mg, was determined to be the recommended Phase 2 and Phase 3 dose for this combination therapy as higher doses were not well tolerated and this dose of dexamethasone is the standard low-dose dexamethasone (40mg weekly or 20mg twice weekly) used with other anti-myeloma drugs including lenalidomide or pomalidomide (and now commonly used with bortezomib and carfilzomib). The patients enrolled in this study had received a median of seven prior lines of therapy, each line typically consisting of two to four separate anti-myeloma agents. All had received prior therapy with at least one proteasome inhibitor, such as carfilzomib or bortezomib, and at least one immunomodulatory agent, such as lenalidomide or pomalidomide, steroids (typically two or more times), while nine of the ten patients also underwent high dose alkylating agent therapy (typically melphalan) with autologous stem cell transplantation. As of December 1, 2014, the best responses among the nine evaluable patients were one stringent complete response (sCR) (11%), five PRs (56%), two MRs (22%) and one PD (11%); one additional patient left the trial after two weeks due to severe infection which was not related to study drug and was therefore not evaluable for response. The clinical benefit response rate (sCR+PR+MR) was 89% and the ORR was 67%. Two of the nine responding patients remain on study as of December 1, 2014. The median duration of response is approximately seven months. Responses in these nine patients are summarized below.

**Patients with Relapsed/Refractory MM Treated with Twice Weekly****Oral Selinexor 45mg/m<sup>2</sup> + Dexamethasone 20mg**

MM Type	Number of Prior therapies	Maximal Change	Response	Study Days
IgG- k	7	-71%	PR	301+
FLC- k	3	-53%	PR	52
FLC- k	5	-99%	sCR	280
IgG- k	9	-84%	PR	170
IgG- k	5	41%	PD	31
IgA- k	10	-55%	PR	121
IgG- k	9	-41%	MR	114
IgG- l	16	-48%	MR	79
IgA- k	6	-82%	PR	201+

+ patients remain on study as of December 1, 2014

Adverse events in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Compared with selinexor given alone, fewer adverse events in patients receiving selinexor in combination with dexamethasone were reported, particularly levels of nausea, vomiting and weight loss. These observations are consistent with dexamethasone's expected reduction in nausea, anorexia and fatigue, which are selinexor's main side effects.

Selinexor with low-dose dexamethasone showed activity with rapid M-protein reductions and good tolerability, even in patients with disease refractory to pomalidomide and/or carfilzomib. We believe that selinexor may have synergistic potential with other MM therapies.

*Advanced or Metastatic Solid Tumor Malignancies*

The International Agency for Research on Cancer estimates that approximately 12.1 million adults were diagnosed with solid tumor malignancies worldwide in 2012. Based on preclinical data and our Phase 1 clinical data in heavily pretreated patients with progressive tumors, we initiated four Phase 2 trials in solid tumor indications: gynecologic malignancies (SIGN study), glioblastoma (KING study), prostate adenocarcinoma (SHIP study) and head and neck, esophageal and lung squamous cell carcinoma (STARRS study). We expect to report preliminary data from some of these studies at various scientific conferences throughout 2015.

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During 2014, we reported data from our ongoing Phase 1 clinical trial of selinexor in patients with advanced or metastatic solid tumor malignancies. All patients entered the study with advanced or metastatic solid tumor cancers relapsed or refractory after multiple previous treatments and objectively progressing on study entry. The primary objectives of the Phase 1 dose escalation trial are to determine the safety, tolerability and recommended Phase 2 dose of orally administered selinexor. These patients were dosed 3-85mg/m<sup>2</sup> (equivalent to approximately 5-145mg) of oral selinexor over a four-week cycle, with lower doses initially given ten times per cycle and higher doses given twice weekly. Response evaluation was done every two cycles in accordance with RECIST.

As of May 13, 2014, 129 patients were enrolled in this Phase 1 clinical trial. Enrolled patients had received a median of three prior therapeutic regimens. Of these patients, 106 were evaluable for response (23 patients were not evaluable or pending evaluation) as of May 13, 2014. Of these evaluable patients, the DCR was 49%. PRs were observed in four patients, one each with colorectal cancer (KRAS mutant), melanoma (BRAF wild type), ovarian adenocarcinoma and cervical cancer. SD was noted in 47 patients, with 17 patients (16%) experiencing SD for six months or longer, which we believe is an indication of clinically significant anti-tumor activity. Eight of nine evaluable patients with hormone and chemotherapy refractory prostate cancer achieved stable disease and have remained on study for between 70 and 317 days. Among 14 evaluable patients with head and neck cancer, nine achieved stable disease with eight on study for 75 to over 401 days. Responses in 106 evaluable patients are summarized below. As of December 1, 2014, there had been no material changes or adverse trends observed in the evaluable solid tumor patient responses.

**Best Responses in Solid Tumor Patients as of May 13, 2014****Cancer**

Type	N	DCR			
		(%)	PR (%)	SD (%)	PD (%)
Colorectal	39	14 (36%)	1 (3%)	13 (33%)	25 (64%)
Head & Neck	14	9 (64%)		9 (64%)	5 (36%)
Prostate	8	7 (88%)		7 (88%)	1 (12%)
Cervical	5	4 (80%)	1 (20%)	3 (60%)	1 (20%)
Ovarian	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
GBM	5				5 (100%)
Melanoma	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Sarcoma	8	7 (88%)		7 (88%)	1 (12%)
Other	19	6 (32%)		6 (32%)	13 (68%)
<b>Total</b>	<b>106</b>	<b>52 (49%)</b>	<b>4 (4%)</b>	<b>48 (45%)</b>	<b>54 (51%)</b>

In addition to the response and disease stabilization summarized above across a variety of different cancer types, biopsies of tumors prior to and three to five weeks after initiation of selinexor treatment are available from some of the patients. These biopsies have confirmed that selinexor treatment induces the nuclear localization of tumor suppressor proteins as well as cancer cell death, or apoptosis, in multiple different cancer types. Given the broadly applicable, unique and confirmed mechanism of action of selinexor, we believe that selinexor has the potential to contribute to the treatment of a large variety of both solid and hematologic cancers. Consistent with this potential, in preclinical models, oral selinexor has shown broad single agent and synergistic or additive activity in combination with many different anti-cancer agents. Therefore, we are initiating a variety of company- and investigator-sponsored combination studies across multiple cancer types. We anticipate that these trials could inform the use of selinexor in earlier stages of cancer therapy across a variety of indications.



Side effects were generally low grade and typically gastrointestinal in nature, or fatigue, similar to those observed in the hematological malignancies, although bone marrow toxicities were less in patients with solid tumors. These common side effects decreased over time, in part due to prophylactic use of standard supportive care. Two dose-limiting toxicities (both reversible) were observed in solid tumor patients receiving 85mg/m<sup>2</sup> dosed twice weekly. Grade 3/4 adverse events occurring in six or more patients in the first cycle included asymptomatic hyponatremia (8%), fatigue (7%), and thrombocytopenia (7%). The most common Grade 1/2 adverse events in the first cycle were nausea (62%), fatigue (52%), anorexia (48%) and vomiting (35%). One

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Grade 3 event was asymptomatic hyponatremia and the other was an acute cerebellar syndrome manifested as ataxia and dysarthria that reversed over several weeks with marked improvement. No other similar central nervous system toxicities were observed in any other patients receiving selinexor to date. Major organ dysfunction or clinically significant cumulative toxicities have not been observed. The intended Phase 2 or Phase 3 trial dose of oral selinexor in solid tumors is 60-80mg twice weekly.

### *Clinical Development Plan*

We have observed preliminary evidence of anti-cancer activity of selinexor across a spectrum of patients with heavily pretreated relapsed and/or refractory cancers. Furthermore, several patients have remained on selinexor for over 12 months, with the longest patient on study for over 24 months. We believe that the fact that patients have remained on selinexor for such periods of time indicates that selinexor has the potential to treat certain relapsed and/or refractory cancers. In addition, because the adverse events observed to date in our Phase 1 clinical trials have generally been lower grades and have been mitigated by supportive care, we believe selinexor is sufficiently well-tolerated to allow patients to remain on therapy for prolonged periods.

In addition to ongoing registration-directed clinical trials of selinexor in AML (SOPRA study), DLBCL (SADAL study) and Richter's (SIRRT study) and the planned trial of selinexor in combination with low-dose dexamethasone in MM that is intended to be registration-directed (STORM study), as well as additional company-sponsored clinical trials of selinexor in MM, we are planning to initiate a Phase 2 clinical trial of selinexor in relapsed and/or refractory peripheral T-cell and cutaneous T-cell lymphomas during the first half of 2015. We expect to initiate additional late-phase clinical trials of selinexor in other hematological malignancies in the future.

In addition to the four ongoing Phase 2 trials in gynecologic malignancies (SIGN study), glioblastoma (KING study), prostate adenocarcinoma (SHIP study) and head and neck, esophageal and lung squamous cell carcinoma (STARRS study), we expect to initiate additional late-phase clinical trials of selinexor in other solid tumor malignancies, including a randomized, registration-directed Phase 2/3 clinical trial of selinexor versus placebo to treat liposarcoma, which we expect to initiate in the second half of 2015. We expect to initiate additional late-phase clinical trials of selinexor in other solid tumor malignancies in the future.

### **Combination Therapy**

Approximately 14.1 million adults worldwide were diagnosed with cancer in 2012, according to the International Agency for Research on Cancer. Based on its mechanism of action and supported by preclinical and clinical data, we believe that selinexor has the potential to be additive or synergistic with approved and experimental therapies in treating many of these 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. In addition to our company-sponsored combination studies in MM, we are evaluating several combination therapies across various indications, largely through ISTs. These include selinexor in combination with:

paclitaxel and carboplatin in advanced ovarian or endometrial malignancies;

irinotecan in adenocarcinoma of stomach and distal esophagus;

low-dose ara-C (LDAC) in AML;

decitabine in AML;

Ara-C and idarubicin in AML;

fludarabine and cytarabine in pediatric leukemia or myelodysplastic syndrome;

ibrutinib in CLL and NHL;

carfilzomib and dexamethasone in MM;

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pegylated liposomal doxorubicin in MM; and

bortezomib and dexamethasone for induction and consolidation in MM.

Data from these combination studies may be presented by our collaborators at scientific conferences or through other publications at various times. We expect such data will inform our Phase 2 and Phase 3 dosing for selinexor in these combinations and allow us to evaluate the combinations with the greatest potential for durable responses and increased survival.

### ***Our Other Drug Candidates***

#### *Topical Selinexor: Topical SINE Compound for Wound Healing*

The inhibition of XPO1 leads to the accumulation of multiple proteins in the nucleus, including anti-inflammatory transcription factors such as I $\kappa$ B and tissue repair proteins such as Nrf2. Nuclear retention of these transcription factors leads to their activation followed by reduced inflammation and activation of tissue repair processes across a variety of animal models of autoimmune and inflammatory conditions. Many of these anti-inflammatory transcription factors also participate in the fibroblast to myofibroblast activation pathway that is crucial for tissue repair. We have observed that the topical administration of selinexor accelerates wound healing and granulation in mouse, rat and pig acute, chronic, diabetic and ischemic wound healing models by reducing the level of edema and inflammation and enhancing the formation of normal scar tissue. Histological analyses of treated wounds in these models showed increased epithelial migration with epithelial closure resulting in smaller wound beds with fewer abscesses and improved cosmesis compared to vehicle control and saline treated wounds.

In light of our preclinical findings, we filed an IND in December 2014 for topical selinexor in wound healing. During the first half of 2015, we plan to initiate a Phase 1b clinical trial of topical selinexor in patients with chronic (non-healing) diabetic foot ulcers. Patients will receive selinexor or placebo gel twice weekly for up to 12 weeks.

#### *Verdinexor (KPT-335): Oral SINE Compound for Viral Indications*

XPO1 regulates the nuclear export of certain viral proteins and is essential for the influenza (and several other viruses) life cycle through regulation of viral ribonucleoprotein (vRNP) nuclear export. We have observed that SINE compounds mediate the inhibition of the nuclear export of influenza vRNP, leading to suppression of *in vitro* and *in vivo* replication of both A and B influenza strains. We have also observed potent activity of verdinexor across a broad panel of strains, including avian influenzas H5N1 and H7N9, consistent with the expectation that SINE compounds will suppress influenza viral replication independent of the origin of the virus. Orally administered verdinexor showed activity in a therapeutic regimen against an H1N1 influenza strain in ferrets and mice with a reduction in lung viral titer to a similar extent as neuraminidase inhibitors such as oseltamivir (Tamiflu<sup>®</sup>). In contrast to existing anti-influenza agents, however, verdinexor also reduced the expression of the pro-inflammatory cytokines IFN- $\gamma$ , IL-1b, IL-6 and TNF- $\alpha$  in H1N1-infected mouse lungs, allowing for the possibility that verdinexor could reduce flu-like symptoms and potentially severe inflammatory reactions, which can be fatal in human infections.

Based upon the anti-influenza activity of verdinexor in animal models, we believe that verdinexor has potential as an effective antiviral and anti-inflammatory therapy for influenza. In the first half of 2015, we expect to file an IND for verdinexor to treat influenza and to initiate a Phase 1 clinical trial in healthy human volunteers.

#### *KPT-350: Oral SINE Compound for Inflammatory and Autoimmune Indications*

As described above, XPO1 mediates the nuclear export of many different cargo proteins. Several of these proteins play key roles in inflammation and related processes. Nuclear factor kB, or NF-kB, is a protein that plays very important roles in many types of inflammation. In cells, NF-kB can be inhibited by another protein

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called I $\kappa$ B, or Inhibitor of NF- $\kappa$ B, that binds to NF- $\kappa$ B and prevents NF- $\kappa$ B from binding to DNA and driving inflammation. When inflammation occurs, XPO1 transports I $\kappa$ B out of the nucleus into the cytoplasm where it cannot inhibit NF- $\kappa$ B activity. When KPT-350 or a similar SINE compound inhibits XPO1, I $\kappa$ B export to the cytoplasm is blocked and I $\kappa$ B accumulates in the nucleus. The I $\kappa$ B in the nucleus binds to NF- $\kappa$ B and blocks its inflammatory (transcriptional) activity. KPT-350 or a similar SINE compound also increases the concentration of other inhibitors of NF- $\kappa$ B in the nucleus including FOXO3a and COMMD1 proteins. Thus, XPO1 inhibition leads to potent, multifaceted inhibition of the inflammatory mediator NF- $\kappa$ B.

KPT-350 and similar SINE compounds have additional important anti-inflammatory activities such as activation of the proteins RXR $\gamma$ , PPAR $\gamma$  and NRF2 (an anti-oxidant, anti-inflammatory and neuroprotective protein). Further, in human patients treated with selinexor, we observed reductions in the numbers of eosinophils, which are white blood cells that are associated with inflammation and allergies.

Our lead indication for KPT-350 is traumatic brain injury, or TBI, as well as autoimmune disorders including multiple sclerosis and system lupus. In animal studies, the gross size of lesions resulting from TBI were dramatically reduced in rats treated with KPT-350. Furthermore, the KPT-350-induced repair site of the injury resulted in healthy tissue with viable neurons. We believe this indicates KPT-350 exerted a neuroprotective effect to prevent permanent neuronal loss due to the blunt force injury.

Our SINE compounds have also shown broad evidence of anti-inflammatory activity across preclinical models of diverse autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. These observations suggest that SINE compounds have multiple anti-inflammatory effects. We are evaluating several SINE compounds, including KPT-350, in additional inflammatory models and preclinical safety studies.

### *PAK4 Inhibitors: Oncology*

In addition to our SINE compounds, we also investigate XPO1 cargo proteins and their role in the cell cycle and cell division. As part of this investigation, we have identified several XPO1 cargo proteins whose inhibition leads to the selective death of cancer cells. One of the XPO1 cargo proteins that we identified was p21-activated kinase 4, or PAK4. PAK4 is member of the PAK family including 6 proteins, PAK1-6. PAK4-6 belong to a growth-promoting sub-family. PAK4 is a signaling protein regulating numerous fundamental cellular processes, including intracellular transport, cellular division, cell shape and motility, cell survival, immune defense and the development of cancer. PAK4 interacts with many key signaling molecules involved in cancer such as beta-catenin, CDC42, Raf-1, BAD and myosin light chain. Based on this biology, we used our drug discovery and optimization expertise to identify small molecule modulators of PAK4. Our PAK4 allosteric modulators have 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 and rat xenograft studies, our PAK4 inhibitors given orally have shown evidence of anti-cancer activity and tolerability. To our knowledge, we are the only company with a pre-IND allosteric, PAK4 specific inhibitor. If we confirm the preliminary results with PAK4 compound in future preclinical studies, we may initiate IND-enabling toxicology studies with one or more PAK4 inhibitors, and may file an IND by the end of 2015.

### *Verdinexor: Oral SINE Compound for Lymphoma in Companion Canines*

We have used spontaneously occurring dog 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 a closely-related, orally available SINE, verdinexor (KPT-335), in dogs with lymphomas. We have received a MUMS designation from the CVM of the FDA for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in dogs with verdinexor.

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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. A Phase 1 clinical trial of verdinexor was performed in dogs with cancer, primarily with lymphoma. The maximum tolerated dose was 35mg/m<sup>2</sup> twice per week although biological activity was observed at 20mg/m<sup>2</sup>. PR or SD, in each case for at least four weeks, was observed in nine out of 14 dogs (64%) with lymphoma with a median time to disease progression of 66 days (range of 35 to 256 days). We performed a dose expansion study in six dogs with lymphoma who were given 30mg/m<sup>2</sup> of verdinexor three times per week; PR or SD was observed in four of the six dogs (67%) with a median time to disease progression of 83 days (range of 35 to 250 days). Side effects included anorexia, weight loss, vomiting and diarrhea and were manageable with dose modulation and supportive care. We conducted an owner observation-based survey and the data indicated that the overall quality of life did not change significantly in dogs treated with verdinexor. Based on these findings, a Phase 2b clinical trial, intended to support regulatory approval under the MUMS designation in the United States, was performed in 58 pet dogs with either newly-diagnosed or first relapse after chemotherapy lymphomas. Verdinexor was administered initially at doses ranging from 25mg/m<sup>2</sup> to 30mg/m<sup>2</sup> 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 who have 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 NADA for verdinexor to the FDA in December 2013. We expect to seek to enter into a collaboration with a third party for the commercialization of verdinexor for dog lymphoma, if we obtain regulatory approval. We believe that verdinexor, if approved, would represent the first oral, targeted therapy for the treatment of dog lymphoma.

The evidence of anti-cancer activity and adverse effect profile of our drug candidate verdinexor in dogs with certain NHL, primarily B and T-cell lymphomas, provided support for our decision to move our closely-related drug candidate selinexor into Phase 1 clinical trials in humans.

## **Intellectual Property**

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

We file patent applications directed to the composition of matter and methods of use and manufacture for our drug candidates. As of February 20, 2015, we were the sole owner of one patent in the United States (issued August 20, 2013 as U.S. Patent No. 8,513,230 and having an expiration date of March 5, 2031) and we had 10 pending patent applications in the United States, seven pending international applications filed under the Patent Cooperation Treaty (PCT), one of which is co-owned with a third party, and 87 pending patent applications in foreign jurisdictions. The PCT is an international patent law treaty that provides a unified procedure for filing a single initial patent application to seek patent protection for an invention simultaneously in each of the member states. Although a PCT application is not itself examined and cannot issue as a patent, it allows the applicant to seek protection in any of the member states through national-phase applications. The technology underlying such pending patent applications has been developed by us and was not acquired from any in-licensing agreement.



The intellectual property portfolios for our key drug candidates as of February 20, 2015 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 28 pending foreign patent

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applications, two pending U.S. non-provisional applications (one of which is allowed) and one pending U.S. provisional application 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 based on the pending provisional application, will expire in 2032, absent any terminal disclaimer, patent term adjustment due to administrative delays by the United States Patent and Trademark Office, or USPTO, or patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. Any patents that may issue in foreign jurisdictions will likewise expire in 2032. We expect to file a non-provisional application claiming the benefit of the pending provisional application in the second half of 2015. Any patents that may issue from such an application will expire no earlier than 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 PCT application that provides the opportunity for seeking protection in all PCT member states. Any patents that may issue in the United States based on this PCT application 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 foreign jurisdictions will likewise expire in 2034.

**KPT-350:** Our KPT-350 patent portfolio covers both the composition of matter and methods of use of KPT-350, and consists of two pending non-provisional U.S. patent applications and 23 pending foreign patent applications. Any patents that may issue in the United States as part of our KPT-350 patent portfolio will expire in 2033, 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 2033.

**PAK4 Inhibitors:** Our PAK4 Inhibitors patent portfolio covers both the composition of matter and methods of use of the PAK4 inhibitors described therein and consists of four patent families with two pending U.S. provisional patent applications and three 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 these PCT applications will expire in 2033 for the earliest filed application and 2034 for the remaining two 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 issued in foreign jurisdictions will likewise expire in 2033 and 2034, respectively. We expect to file a non-provisional patent application claiming the benefit of the provisional application in the fourth family in the second half of 2015. Any patents that may issue from such application will expire no earlier than 2035.

**Verdinexor (KPT-335):** Our selinexor patent portfolio described above, with the exception of the pending provisional application, also covers both the composition of matter and methods of use of verdinexor, as well as methods of making verdinexor.

In addition to the patent portfolios covering our key drug candidates, as of February 20, 2015, our patent portfolio also includes one patent that was issued August 20, 2013 as U.S. Patent No. 8,513,230 and pending patent applications 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 on January 20, 2015 as Registration Nos. 4,676,255 and 4,676,226. The mark

for our logo was registered February 24, 2015 as Registration No. 4,693,100. In September and October of 2014 we filed seven additional Intent to Use Trademark Applications, six for drug names for selinexor and one for the term SINE .

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

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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 patent 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, no other company has an XPO1 inhibitor in clinical development at the present time. However, Stemline Therapeutics, Inc. announced in January 2015 that it had exclusively licensed the rights to develop and commercialize SL-801, an XPO1 inhibitor, from CanBas Co., Ltd. The compound is in preclinical development and Stemline has indicated its intent to file an IND in 2015.

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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 level of generic competition 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 competitive generic drugs.

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 not be competitive 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.

### *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 decitabine (Dacogen<sup>®</sup>, Otsuka) or azacitadine (Vidaza<sup>®</sup>, 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. A number of anti-cancer agents (often in combination) are being investigated in this population, including but not limited to, midostaurin (Novartis), quizartinib (Daiichi Sankyo), volasertib (Boehringer Ingelheim), SGI-110 (Otsuka/Astex), sapacitabine (Cyclacel), and CPX-351 (Celator).

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### *Diffuse Large B-Cell Lymphoma (DLBCL)*

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan<sup>®</sup>, 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<sup>®</sup>, Pharmacyclics) and the immunomodulatory drug lenalidomide (Revlimid<sup>®</sup>, 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, obinutuzumab (Gazyva<sup>®</sup>, Roche) everolimus (Afinitor<sup>®</sup>, Novartis), lenalidomide (Revlimid<sup>®</sup>, Celgene), ofatumumab (Arzerra<sup>®</sup>, GSK), and ibrutinib (Imbruvica<sup>®</sup>, Pharmacyclics). In addition, chimeric antigen receptor T-cell therapies or CAR-T therapies, are currently in clinical development for the treatment of DLBCL by companies including Novartis, Juno and Kite, and may present future competition.

### *Richter's Transformation*

Although there are no specific therapies approved to treat Richter's transformation, multi-agent chemoimmunotherapy is typically used as a first line treatment.

### *Multiple Myeloma (MM)*

Over the past 12 years, six agents have been approved in the U.S. for the treatment of patients with MM: bortezomib (Velcade<sup>®</sup>, Takeda), lenalidomide (Revlimid<sup>®</sup>, Celgene) thalidomide (Thalomid<sup>®</sup>, Celgene), carfilzomib (Kyprolis<sup>®</sup>, Amgen), pomalidomide (Pomalyst<sup>®</sup>, Celgene), and most recently, panobinostat (Farydak<sup>®</sup>, Novartis), which was approved by the FDA in February 2015. 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 such as vorinostat (Zolinza<sup>®</sup>, Merck), ixazomib (Takeda), plitidepsin (PharMar), elotuzumab (BMS), masitinib (AB Sciences), and daratumumab (Janssen).

### *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. The compound is in preclinical development and Stemline indicated its intent to file an IND in 2015. Additionally, Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb Company) has evaluated compounds derived from leptomyacin B in preclinical studies. To our knowledge, the Kosan compounds are not currently being developed.

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, as in cancer, there are no other XPO1 inhibitors in clinical development for the treatment of any other diseases, including indications like 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 Inhibitors***

Our PAK4 inhibitors, 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. 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

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that compound had poor oral bioavailability in both animals and humans, and, to our knowledge, its 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.

## **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, 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 drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant 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 DOJ, 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:

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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 investigational new drug application, or 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;

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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 a new drug application, or 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 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 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.

*Human Clinical Studies 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 objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin.

In addition, 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 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. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their [ClinicalTrials.gov](http://ClinicalTrials.gov) website.

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

Phase 1: The drug is initially introduced into 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.

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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.

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.

### *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 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.

### *Submission of an NDA to the FDA*

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to 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 additionally subject to an application user fee, currently exceeding \$2.1 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding \$104,000 per product and \$554,000 per establishment. These fees are typically increased annually.

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The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74<sup>th</sup> day after 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 FDA accepts it for filing. Once the submission is accepted for filing, FDA begins an in-depth substantive review. The FDA has agreed to specified 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 FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. These pre-approval inspections 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.

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 is required to 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 and Priority Review 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 fast track designation, breakthrough therapy designation and priority review 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 drugs, 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 NDA 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 NDA 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, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or

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FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as breakthrough therapies. A product 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, 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 drug 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 drug 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 drug 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.

### *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,

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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

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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 marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

*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. Physicians 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 physician 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. In cases where such exclusivity has been granted, an ANDA may not be filed with 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

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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.

### *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.

### *Pediatric Studies and Exclusivity*



Under the Pediatric Research Equity Act of 2003, a 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, FDA, and 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.

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.

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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 accept or approve another application.

### *Orphan Drug Designation and Exclusivity*

Under the Orphan Drug Act, 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 a NDA. If the request is granted, 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 entitled to orphan product exclusivity. Orphan product exclusivity means that 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.

### *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 Amendments, 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 a NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

### *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 drug 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

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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.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union 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 European Union 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 European Union 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 European Union 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 European Union, 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 European Union member states where such product has not received marketing approval in any European Union 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.



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### *Data and Market Exclusivity in the European Union*

In the European Union, 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 European Union 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.

### *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 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).

### *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.

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***Pharmaceutical Coverage, Pricing and Reimbursement***

Significant uncertainty exists as to the coverage and reimbursement status of products approved by FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. 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 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. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. 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 has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

As a result, the marketability of any product which receives regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products that receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In the European Union, 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 European Union 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. European Union 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 health care 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.

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***Healthcare Law and Regulation***

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment 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, imposes criminal and civil liability for executing 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, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

the federal transparency requirements under the Health Care Reform Law will require manufacturers of drugs, biologics, devices and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

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

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug

manufacturers to report information related to payments to physicians and other health care 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.

***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.

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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, adverse events or unexpected results must also be produced in accordance with the relevant regulatory requirements.

## **Employees**

As of February 28, 2015, we had 71 full-time employees, 54 of whom were primarily engaged in research and development activities and 21 of whom had an M.D. or Ph.D. degree.



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The following table lists the positions, names and ages of our executive officers as of March 1, 2015:

<b>Name</b>	<b>Age</b>	<b>Position</b>
Michael G. Kauffman, M.D., Ph.D.	51	Chief Executive Officer and Director
Sharon Shacham, Ph.D., M.B.A.	44	President and Chief Scientific Officer
Justin A. Renz, C.P.A., M.S.T., M.B.A.	43	Executive Vice President, Chief Financial Officer and Treasurer
Ran Frenkel, RPh.	46	Executive Vice President, Worldwide Development Operations
Christopher B. Primiano, J.D., M.B.A.	34	Vice President, Corporate Development, 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 and compensation committee of Verastem Inc., a public biopharmaceutical company, and on the board of directors and the compensation committee of Metamark Genetics Inc., a private molecular diagnostics 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

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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.

*Justin A. Renz, C.P.A., M.S.T., M.B.A.* Mr. Renz joined Karyopharm in August 2014 as Executive Vice President and Chief Financial Officer. Prior to joining Karyopharm, Mr. Renz served most recently as Executive Vice President, Chief Financial Officer and Treasurer at Zalicus Inc. (formerly CombinatoRx, Inc.), a biopharmaceutical company, which he joined in September 2006. Mr. Renz led core business and finance functions at Zalicus, oversaw multiple rounds of equity and debt financing and led the company's asset monetization strategy. More recently, Mr. Renz was instrumental in the reverse merger and sale of Zalicus to EPIRUS Biopharmaceuticals Inc. in July 2014. Prior to Zalicus, Mr. Renz served in senior finance and accounting roles at Serono, Inc. and Coley Pharmaceutical Group, Inc. Earlier in his career, Mr. Renz held increasingly senior finance positions at ArQule, Inc. and Millipore Corporation. Mr. Renz began his career with Arthur Andersen LLP in 1993. Mr. Renz received a B.A. in Economics and Accounting from the College of the Holy Cross, an M.S. in Taxation from Northeastern University and an M.B.A. from Suffolk University.

*Ran Frenkel, RPh.* Mr. Frenkel was appointed Executive Vice President, Worldwide Development Operations of Karyopharm in October 2014. 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 and is Vice President, Corporate Development, General Counsel and Secretary. 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, 2<sup>nd</sup> Floor, Newton, Massachusetts 02459. Our telephone number is (617) 658-0600, and our website is located at [www.karyopharm.com](http://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.





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**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. In addition, we regularly use our website to post information regarding our business, development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors" as a source of information about us.

Our Code of Business Conduct and Ethics, Corporate Governance Guidelines and the charters of the Audit, Compensation 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, 2<sup>nd</sup> floor, Newton, Massachusetts 02459, U.S.A.

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**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 we do not expect to 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 United States 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 a third party 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 future 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.

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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 have limited experience in designing clinical trials and 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 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, which trials we refer to as registration-directed clinical trials. 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. In addition, 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 limited discussions with the FDA and non-U.S. regulatory authorities regarding the design of our planned registration-directed clinical trials for selinexor. We commenced three such clinical trials of selinexor during 2014 and plan to initiate at least one registration-directed clinical trial in 2015. We plan to seek regulatory approvals of selinexor in North America and Europe in each indication with respect to which such registration-directed clinical trial is being conducted and with respect to which we receive positive results and we may seek such approvals in other geographies. We cannot be certain that we will commence or complete these trials as anticipated and 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 registration-directed 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 Phase 1 or Phase 2 clinical trials that may be required prior to commencing our planned registration-directed clinical trials, or additional clinical trials following completion of our current and planned registration-directed 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 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 the primary endpoint in any randomized registration-directed clinical trials of selinexor 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 registration-directed clinical trial that is not randomized may be different. For example, the primary endpoint of our randomized registration-directed clinical trial of selinexor in

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patients over 60 years of age with AML in first relapse, who are not candidates for intensive chemotherapy or transplantation, is overall survival. We have no clinical data in humans relating to the impact of selinexor on overall survival. We have no comparative clinical data between selinexor and standard or 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 registration-directed clinical trial of selinexor in patients with Richter's Syndrome and DLBCL. These clinical trials will not be randomized against control arms as there are no generally accepted second-line treatments for Richter's Syndrome or third-line treatments for DLBCL and, therefore, no available therapies to serve as a control arm for the trial. Consequently, the primary endpoints of these trials are overall response rate. If selinexor does not demonstrate sufficient overall response rates for Richter's Syndrome or DLBCL, 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, it will likely not be approved for that indication.

***We are very early in our development efforts and have only one drug candidate in clinical development. All of our other drug candidates are still in preclinical 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 very early in our development efforts and have only one drug candidate, selinexor, in clinical development. The success of selinexor and any of our other drug candidates will depend on several factors, including the following:

successful completion of preclinical 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, and possibly 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.



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***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 or current clinical-stage cancer drug candidates 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 proving 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, the results of 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

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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 future collaborators that 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.

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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 or allow our competitors to bring drugs to market before we do and impair our ability to successfully commercialize our drug candidates and may harm our business and results of operations.

***If we experience delays or difficulties in the enrollment of patients in 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;

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.

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.***

Our lead drug candidate selinexor is in clinical development and our other drug candidates are in preclinical development. 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 Phase 1 and Phase 2 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

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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 adverse events 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 receive 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



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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 enter into 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 do not have a sales or marketing infrastructure and have no experience in the sale or marketing of pharmaceutical drugs. To date, we have not entered into a strategic collaboration that provides us with access to a collaborator's resources in selling or marketing drugs. To achieve commercial success for any approved drug for which sales and marketing is not the responsibility of any strategic collaborator that we 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 some of our drug candidates if and when they are approved, or enter into collaborations with respect to the sale and marketing of our drug candidates. We currently intend to establish a corporate infrastructure to enable us to independently market selinexor in North America and Western Europe.

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.

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If we enter into arrangements with third parties to perform sales and marketing services, our revenues from the sale of drug or the profitability of these revenues to us are likely to be lower than if we were to market and sell any drugs that we develop ourselves. In addition, we may not be successful in entering into 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 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.

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 become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.***

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval

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requirements in ways that could involve additional costs and cause delays in obtaining approvals. 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. As a result, we might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay our commercial launch of the drug, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

Our ability to commercialize any drugs successfully also 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. 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. 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. 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 to 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 purposes for which the drug is approved by the FDA or similar 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;

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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.

***Verdinexor (KPT-335) is our clinical drug candidate for the treatment of pet dogs with newly-diagnosed and first time relapse lymphomas. If the results of our clinical trials of verdinexor are not viewed positively or verdinexor is not approved by the FDA, this may raise safety and efficacy concerns for selinexor, as the anti-cancer activity and adverse event profile of verdinexor in dogs with lymphomas provided support for our decision to move selinexor into Phase 1 clinical trials.***

As part of the drug discovery and development process, we have used spontaneously occurring pet dog cancers as a surrogate model for human malignancies. Dog lymphomas respond to chemotherapy in a manner similar to their human counterparts (human non-Hodgkin's lymphomas) and display a comparable genetic profile. The anti-cancer activity of our drug candidate verdinexor (KPT-335) in a Phase 1 clinical trial in dogs with certain lymphomas provided support for our decision to move selinexor, our closely-related human drug candidate, into Phase 1 clinical trials. We conducted a Phase 2b clinical trial of verdinexor in dogs with newly-diagnosed or first time relapse lymphomas. We have received a Minor Use / Minor Species, or MUMS, designation from the Center for Veterinary Medicine of the FDA for the treatment of newly-diagnosed or after first relapse lymphomas in dogs with verdinexor. Our Phase 2b clinical trial was intended to support regulatory approval under the MUMS designation. We submitted and the FDA accepted the safety and effectiveness sections of a NADA for verdinexor. If verdinexor fails to show adequate safety or efficacy or is not otherwise viewed positively or if verdinexor is not otherwise approved by the FDA for the treatment of lymphomas in dogs, this may raise questions regarding selinexor because we have used dog cancers as a surrogate model for human malignancies. In such an event, verdinexor's clinical trial results may cause the FDA or non-U.S. regulatory authorities to require more information, including additional preclinical or clinical data to support approval of selinexor. If the results of the Phase 2b clinical trial of verdinexor fail to demonstrate safety and efficacy to the satisfaction of the FDA or are not otherwise viewed positively, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of verdinexor. In such an event, we also may not be able to realize our potential to generate revenue from the commercialization of verdinexor, either on our own or with a collaborator.

***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;



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unexpected changes in tariffs, trade barriers and regulatory requirements;

economic weakness, including inflation, 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 \$75.8 million and \$33.9 million for the years ended December 31, 2014 and December 31, 2013, respectively. As of December 31, 2014 and December 31, 2013, we had accumulated deficits of \$138.3 million and \$62.6 million, respectively. We have not generated any revenue to date from sales of any drugs and have financed our operations principally through sales of equity in private placements, our initial public offering, or IPO, and two follow-on offerings of our common stock, including our most recent offering in January 2015. We have devoted substantially all of our efforts to research and development. Our lead drug candidate, oral selinexor (KPT-330), as well as the topical formulation of selinexor, are in clinical development and our other drug candidates for the treatment of human disease are expected to begin clinical development in 2015 or are in preclinical 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;

identify additional drug candidates;

initiate additional clinical trials for our drug candidates;

seek marketing approvals for any of our drug candidates that successfully complete clinical trials;

ultimately establish sales, marketing, manufacturing and distribution infrastructure to commercialize any drugs for which we may obtain marketing approval;

maintain, expand and protect our intellectual property portfolio;

hire additional clinical, quality control and scientific personnel;

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 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

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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 are an early-stage company. We were incorporated in December 2008 and commenced operations in the first half of 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-stage clinical trials of our drug candidates. Our lead drug candidate is currently in multiple Phase 1 and Phase 2 clinical trials and all of our other drug candidates for the treatment of human disease are in preclinical development. We have not yet demonstrated our ability to successfully complete any late-stage 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 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, restricted cash and investments will enable us to fund our operating expenses and capital expenditure requirements into 2018. 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;

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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 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 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.***

As has been widely reported, global credit and financial markets have experienced extreme disruptions over some of the past several years, including severely 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

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

We intend to seek third-party collaborators for certain aspects of the development, marketing and/or commercialization of our drug candidates. For example, while we currently plan to make regulatory filings and to commercialize and market selinexor in North America and Western Europe with respect to the potential approval of selinexor without a collaborator, we anticipate that we will seek to enter into a collaboration for marketing and commercialization of selinexor at the appropriate time in the future for other geographies. In addition, we intend to seek one or more collaborators to aid in the further development, marketing and/or commercialization of selected SINE compounds for inflammatory conditions, viral disorders and wound healing. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. If we do enter into any such arrangements with any 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;



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collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;

disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our drugs or drug candidates or that result in costly litigation or arbitration that diverts management's attention and resources of 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 future collaborators or acquirers.

Collaboration agreements may not lead to development or commercialization of drug candidates in the most efficient manner, or at all.

***If we are not able to establish 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 collaborate with 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.

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***We rely on third parties to 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 third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to 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 European Medicines Agency 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 intend to 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 intend to rely on academic and private non-academic institutions to conduct and sponsor clinical trials relating to selinexor and our other drug candidates. We will not control the design or conduct of the investigator-sponsored trials, and it is possible that the FDA or non-U.S. regulatory authorities will not view these investigator-sponsored trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results.

Such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from the investigator-sponsored trials. However, we do not have control over the timing and reporting of the data from investigator-sponsored trials, nor do we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of our drug candidates. Further, if

investigators or institutions breach their obligations with respect to the clinical development of our drug candidates, or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

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Additionally, the FDA or non-U.S. regulatory authorities may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or 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 (fill-and-finish) 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 future 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 specifications;

the possible failure of the third party to manufacture our drug candidate according to our schedule, or at all;

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 cGMP regulations or similar regulatory requirements outside of the United States. 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.

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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, one patent has issued that relates to XPO1 inhibitors, other than our key drug candidates, and their use in targeted therapeutics. We cannot be certain that any 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 patent 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.



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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 future collaborators that we may have 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; however, if we are found to infringe a third party's intellectual property rights, we could be required 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

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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

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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.

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

Although we filed three intent to use applications with respect to our trademarks in the United States in August 2013 and seven intent to use applications during September and October of 2014, only three of our trademarks have been registered with registration limited to the U.S. The remainder of our trademarks are not yet registered in the United States or other countries. 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. We have also not yet registered trademarks for any of our drug candidates in any jurisdiction. When we file trademark

applications for our drug candidates those applications may not be allowed for

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registration, and registered trademarks may not be obtained, maintained or enforced. 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 Other Legal Compliance Matters**

*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 for a product, 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 the same 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.

*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



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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.

***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 collaborators we may have in the future, 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 collaborators we may have in the future, 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 collaborators we may have in the future, 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 collaborators we may have 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 any collaborators we may have in the future, 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 any

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collaborators we may have in the future, 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.

***Even if we, or any collaborators we may have in the future, 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 any collaborators we may have in the future, 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 any collaborators we may have in the future, 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 future 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 future collaborators, receive marketing approval for one or more of our drug candidates, we, and our future 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 future collaborators, are not able to comply with post-approval regulatory requirements, we, and our future collaborators, could have the marketing approvals for our drugs withdrawn by regulatory authorities and our, or our future 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 future collaborators, obtain marketing approval in the future could be subject to post-marketing restrictions or withdrawal from the market and we, and our future 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 future 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

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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 future 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 Federal Food, Drug, and Cosmetic Act 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 adverse events 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.

***Recently-enacted and future legislation may increase the difficulty and cost for us and our future collaborators to obtain marketing approval of 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 prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of our future 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 be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or our future collaborators, may receive for any approved drugs.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products and could decrease the coverage

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and price that we, or our future collaborators, may receive for any approved drugs. While the MMA only addresses drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

More recently, in March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA.

Among the provisions of the PPACA of potential importance to 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 False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;

a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;

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 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.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. 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 drug candidates for which marketing approval is obtained.

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

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our drug candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and our future collaborators to more stringent drug labeling and post-marketing testing and other requirements.



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*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.

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***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

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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, particularly 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 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

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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 these persons could impede the achievement of our research, development and commercialization 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.

***Michael Kauffman, M.D., Ph.D. and Sharon Shacham, Ph.D., M.B.A. are married. 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. 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 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, potentially, 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.***

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 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.



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**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, 2014, 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

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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. 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

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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 for up to five years. 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, 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. In this report, we have not included, and will not include in our proxy statement, all of the executive compensation related information that would be required if we were not an emerging growth company. 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.

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Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or 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

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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 32,710,790 shares outstanding as of December 31, 2014. Of such shares, at least 12.0 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 approximately 15.8 million shares of our common stock as of December 31, 2014 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). 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 that may have resulted in ownership changes under Sections 382 and 383 of the Code. In addition, future changes



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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 prior to the expiration of our net operating loss and tax credit carryforwards.

**Item 1B. Unresolved Staff Comments**

None.

**Item 2. Properties**

Our headquarters are located in Newton, Massachusetts, where we occupy approximately 29,933 square feet of office and laboratory space. In order to accommodate our expected need for additional office and laboratory space we amended our Newton, Massachusetts lease for an additional 16,234 square feet which we will begin to occupy in 2015.

**Item 3. Legal Proceedings**

We are not a party to any material legal proceedings.

**Item 4. Mine Safety Disclosures**

Not applicable.

**Table of Contents****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 for the fourth quarter of fiscal 2013, from November 6, 2013, the date on which our common stock first began trading on the NASDAQ Global Select Market, through December 31, 2014, as reported on the NASDAQ Global Select Market:

	<b>Year Ended December 31, 2013</b>	
	<b>High</b>	<b>Low</b>
Fourth Quarter (from November 6, 2013)	\$ 25.69	\$ 15.50

  

	<b>Year Ended December 31, 2014</b>	
	<b>High</b>	<b>Low</b>
First Quarter	\$ 47.87	\$ 21.13
Second Quarter	\$ 47.98	\$ 23.86
Third Quarter	\$ 47.89	\$ 32.97
Fourth Quarter	\$ 49.01	\$ 29.24

**Holdings**

As of March 11, 2015, there were 10 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.

**Table of Contents****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, 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, all through December 31, 2014. 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
<b>Karyopharm Therapeutics Inc.</b>	<b>100.00</b>	<b>142.80</b>	<b>233.21</b>
<b>NASDAQ Composite</b>	<b>100.00</b>	<b>106.84</b>	<b>121.45</b>
<b>NASDAQ Biotechnology</b>	<b>100.00</b>	<b>108.50</b>	<b>143.80</b>

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, as amended, 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 Securities Exchange Act, except to the extent we specifically incorporate it by reference into such a filing.

**Recent Sales of Unregistered Securities**

None.

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**Use of Proceeds from Registered Securities**

On November 12, 2013, we issued and sold 6,800,000 shares of our common stock in the IPO at a public offering price of \$16.00 per share, for aggregate gross proceeds of \$108.8 million. On December 10, 2013, we issued and sold 1,020,000 shares of our common stock pursuant to the underwriters' full exercise of their option to purchase additional shares in the IPO at \$16.00 per share for gross proceeds of \$16.3 million. All of the shares issued and sold in the IPO were registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-191584), which was declared effective by the SEC on November 5, 2013, and a Registration Statement on Form S-1 (File No. 333-192110) filed pursuant to Rule 462(b) of the Securities Act. Merrill Lynch, Pierce, Fenner & Smith Incorporated and Leerink Swann LLC acted as joint-book-running managers of the offering and as representatives of the underwriters. JMP Securities LLC and Oppenheimer & Co. Inc. acted as co-managers for the offering. The offering commenced on November 5, 2013 and terminated upon sale of all of the shares offered.

The net offering proceeds to us, after deducting underwriting discounts of \$8.8 million and offering expenses payable by us totaling \$3.2 million, were approximately \$113.2 million. No offering expenses or net offering proceeds were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates.

As of December 31, 2014, we have used approximately \$57.2 million of such net offering proceeds to fund the continued clinical development of our lead drug candidate, selinexor, the preclinical development of our drug candidates for anti-inflammatory, viral and wound healing indications, the discovery, research and preclinical development of additional drug candidates and for working capital and other general corporate purposes. We are holding a significant portion of the balance of the net proceeds from the offering in interest-bearing money market accounts, prime money market funds and other short-term investments. There has been no material change in our planned use of the balance of the net proceeds from the offering described in the prospectus filed by us with the SEC pursuant to Rule 424(b)(4) on November 7, 2013.

**Table of Contents****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.

	<b>Years Ended December 31,</b>			
	<b>2014</b>	<b>2013</b>	<b>2012</b>	<b>2011</b>
	<b>(In thousands, except share and per share amounts)</b>			
<b>Consolidated Statement of Operations Data:</b>				
Contract and grant revenue	\$ 229	\$ 387	\$ 634	\$ 152
Operating expenses:				
Research and development	60,127	28,452	14,095	8,623
General and administrative	15,948	5,885	2,429	1,840
Total operating expenses	76,075	34,337	16,524	10,463
Loss from operations	(75,846)	(33,950)	(15,890)	(10,311)
Other income/(expense), net	69	3	2	
Net loss	\$ (75,777)	\$ (33,947)	\$ (15,888)	\$ (10,311)
Net loss per share applicable to common stockholders - basic and diluted	\$ (2.43)	\$ (5.59)	\$ (8.95)	\$ (10.27)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	31,135,694	6,067,679	1,775,323	1,004,144
	<b>2014</b>	<b>As of December 31,</b>		<b>2011</b>
		<b>2013</b>	<b>2012</b>	
		<b>(in thousands)</b>		
<b>Consolidated Balance Sheet Data:</b>				
	\$ 205,724	\$ 155,974	\$ 391	\$ 6,512

Cash, cash equivalents and short-term investments				
Working capital	195,450	154,664	(976)	4,749
Total assets	220,337	158,226	1,311	7,224
Total preferred stock and preferred stock subscription			27,258	17,758
Total stockholders' equity (deficit)	206,794	154,934	(27,877)	(12,651)

### **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.

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**Business Overview**

**Overview**

We are a clinical-stage pharmaceutical company founded in December 2008 by Dr. Sharon Shacham. We are focused on the discovery and development of novel first-in-class drugs directed against nuclear transport targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on the understanding of the regulation of intracellular transport between the nucleus and the cytoplasm. We have discovered and developed novel, small molecule, **S**elective **I**nhibitors of **N**uclear **E**xport, or **SINE**, compounds that inhibit the nuclear export protein XPO1. We have worldwide rights to these SINE compounds. Our lead drug candidate, selinexor (KPT-330), is an XPO1 inhibitor being evaluated in multiple open-label Phase 1 clinical trials in patients with heavily pretreated relapsed and/or refractory hematological and solid tumor malignancies. To date, we have administered selinexor to over 600 patients in these trials. Preliminary evidence of anti-cancer activity has been observed in some patients and selinexor has been sufficiently well-tolerated to allow many of these patients to remain on therapy for prolonged periods, including several who have remained on study for over 12 months. To our knowledge, no other XPO1 inhibitors are in clinical development at the present time.

We have devoted substantially all of our efforts to research and development. 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. To date, we have financed our operations primarily with the net proceeds from the private placements of our preferred stock and the net proceeds from our initial public offering.

As of December 31, 2014, we had an accumulated deficit of \$138.3 million. We had net losses of \$75.8 million, \$33.9 million and \$15.9 million for the years ended December 31, 2014, 2013 and 2012, 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;

identify additional 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;

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 operations as a public company.

## **Financial Overview**

### ***Revenue Recognition***

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



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To date, our only revenue is from 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 conduct clinical trials and preclinical studies;

the cost of acquiring, developing and manufacturing clinical trial materials;

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. We expect to begin to track costs by project when drug candidates other than selinexor enter clinical trials in humans.

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.

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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 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 prospectus, 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.

### ***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

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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, or CROs, and contract manufacturing organizations, or 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 and restricted stock. We account for our stock-based awards to employees in accordance with Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 718, *Compensation Stock Compensation*, or 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. Since there was no public market for our common stock prior to our initial public offering, we lacked company specific historical and implied volatility data. In addition, as a newly public company, we do not have sufficient history to estimate the volatility of our common stock price or the expected life of the options. Therefore, we base our estimate of expected volatility 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

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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.

We are also required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from estimates. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those options that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on options that ultimately vest.

**Results of Operations**

The following table summarizes our results of operations for the years ended December 31, 2014, 2013 and 2012:

	<b>Years Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
	<b>(in thousands)</b>		
Contract and grant revenue	\$ 229	\$ 387	\$ 634
Operating expenses:			
Research and development	60,127	28,452	14,095
General and administrative	15,948	5,885	2,429
Loss from operations	(75,846)	(33,950)	(15,890)
Other income, net	69	3	2
Net loss	\$ (75,777)	\$ (33,947)	\$ (15,888)

**Comparison of Years Ended December 31, 2014 and 2013**

**Contract and Grant Revenue.** We recognize revenue pursuant to a sponsored research agreement. Contract and grant revenue for the year ended December 31, 2014 was \$0.2 million compared to \$0.4 million for the year ended December 31, 2013. The decrease in revenue was the result of recognizing less revenue pursuant to grant funding during the year ended December 31, 2014.

**Research and Development Expense.** Research and development expense increased by approximately \$31.6 million to \$60.1 million for the year ended December 31, 2014 from \$28.5 million for the year ended December 31, 2013. The increase primarily related to:

an increase of \$14.7 million in clinical trial costs, primarily related to an increase of approximately \$10.6 million in costs to CROs, and an increase of \$6.9 million in costs related to the manufacture of selinexor, partially offset by a decrease of \$2.8 million related to the manufacture of verdinexor;

an increase of \$6.3 million in personnel costs, primarily due to an increased headcount and an increase of \$3.1 million in stock-based compensation expense related to equity awards granted to personnel, primarily related to the higher fair value of our common stock;

an increase of \$4.3 million in consulting fees, primarily due to an increase of \$2.8 million paid to consultants and an increase of \$1.5 million in stock-based compensation expense related to equity awards granted to consultants, primarily due to the higher fair value of our common stock;

an increase of \$4.0 million in preclinical efficacy and toxicology study costs;



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an increase of approximately \$1.1 million in discovery work, including preclinical studies and screening;

a decrease of approximately \$1.0 million in costs related to our clinical trials of verdinexor in pet dogs.

*General and Administrative Expense.* General and administrative expense increased by approximately \$10.0 million to approximately \$15.9 million for the year ended December 31, 2014 from approximately \$5.9 million for the year ended December 31, 2013. The increase is primarily related to:

an increase of approximately \$4.7 million in personnel costs, primarily due to increased headcount and an increase of approximately \$3.3 million in stock-based compensation expense related to equity awards granted to personnel, primarily related to the higher fair value of our common stock;

an increase of approximately \$2.8 million in consulting fees, primarily related to an increase in stock-based compensation expense related to equity awards granted to consultants, primarily due to the higher fair value of our common stock, partially offset by decreases in costs for consultants related to finance and business development;

an increase of approximately \$2.0 million in professional fees, primarily related to higher legal fees for protecting our intellectual property, higher corporate legal fees, and higher public and investor relations fees and other fees to operate as a public company; and

an increase of approximately \$0.5 million in insurance expense, primarily due to our becoming a publicly traded company.

*Other Income (Expense), net.* Other income (expense), net was less than \$0.1 million for all periods presented.

***Comparison of Years Ended December 31, 2013 and 2012***

*Contract and Grant Revenue.* Contract and grant revenue decreased by \$0.2 million to \$0.4 million in 2013 from \$0.6 million in 2012. The decrease in revenue was the result of recognizing fewer milestones during 2013 associated with a grant.

*Research and Development Expense.* Research and development expense increased by \$14.4 million to \$28.5 million in 2013 from \$14.1 million in 2012. The \$14.4 million increase is primarily related to:

an increase of \$8.3 million in clinical trial costs, including a \$3.2 million increase in the cost of the active pharmaceutical ingredient and finished drug product,

an increase of \$2.7 million in consulting fees, including a \$1.5 million increase in stock-based compensation expense related to equity grants to consultants, primarily due to the higher fair value of our common stock,

an increase of \$1.5 million in personnel costs, primarily due to increased headcount and a \$0.4 million increase in stock-based compensation expense related to equity grants to personnel, primarily related to the higher fair value of our common stock, and

an increase of \$1.4 million in discovery work, including preclinical studies and screening.

*General and Administrative Expense.* General and administrative expense increased by \$3.5 million to \$5.9 million for 2013 from \$2.4 million for 2012. The \$3.5 million increase is primarily related to:

an increase of \$1.2 million in consulting fees, primarily related to business development, investor relations and financial services, including a \$0.5 million increase in stock-based compensation expense related to equity grants to consultants, primarily due to the higher fair value of our common stock,

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an increase of \$1.1 million in personnel costs, primarily due to increased headcount and an increase of \$0.6 million in stock-based compensation expense related to equity grants to personnel, primarily due to the higher price of our common stock,

an increase of \$0.7 million in professional fees, primarily related to higher corporate legal fees and audit fees,

an increase of \$0.1 million in insurance expense, primarily due our becoming a publicly traded company, and

an increase of \$0.1 million in travel expenses.

**Liquidity and Capital Resources**

To date, we have not generated any material revenues. We have financed our operations to date principally through private placements of our preferred stock and proceeds from our initial public offering and follow-on offerings.

As of December 31, 2014, we had \$214.8 million in cash, cash equivalents, restricted cash and investments. In July 2014, we completed a public offering of 2,844,334 shares of our common stock at a public offering price of \$42.50 per share. We received net proceeds of approximately \$112.8 million, after deducting underwriting discounts, commissions and expenses payable by us. 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 \$90.9 million, after deducting the underwriting discount and estimated offering expenses payable by us.

**Cash flows**

The following table provides information regarding our cash flows:

	<b>Years Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
	<b>(in thousands)</b>		
Net cash used in operating activities	\$ (51,447)	\$ (30,290)	\$ (15,509)
Net cash used in investing activities	(67,031)	(57)	(121)
Net cash provided by financing activities	113,121	185,930	9,509
Effect of exchange rate changes	(8)		
Net (decrease) increase in cash and cash equivalents	\$ (5,365)	\$ 155,583	\$ (6,121)

***Net Cash Used in Operating Activities***

Net cash used in operating activities was \$51.4 million during the year ended December 31, 2014 compared to \$30.3 million during the year ended December 31, 2013. The \$21.1 million increase in cash used in operating activities during the year ended December 31, 2014 was driven primarily by an increase in our net loss adjusted for

non-cash charges and changes in the components of working capital due to an increase in research and development expenses as we increased our research and development headcount and increased spending on external research and development costs related to selinexor.

Net cash used in operating activities was \$30.3 million during the year ended December 31, 2013 compared to \$15.5 million during the year ended December 31, 2012. The increase in cash used in operating activities during the year ended December 31, 2013 was driven primarily by an increase in our net loss and by changes in components of working capital, including an increase in prepaid expenses and other current assets.

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### ***Net Cash Used in Investing Activities***

Net cash used in investing activities was \$67.0 million during the year ended December 31, 2014. The cash used in investing activities for the year ended December 31, 2014 reflects an increase of \$63.8 million in purchases of investments, \$0.4 million in restricted cash related to a facility lease and the purchase of \$2.8 million of property and equipment related to the renovation of and relocation to new office and laboratory space. There was less than \$0.1 million in investing activities for the year ended December 31, 2013.

Net cash used in investing activities was approximately \$0.1 million during the years ended December 31, 2013 and December 31, 2012. The cash used in investing activities was for the purchase of property and equipment.

### ***Net Cash Provided by Financing Activities***

Net cash provided by financing activities was \$113.1 million during the year ended December 31, 2014 compared to \$185.9 million during the year ended December 31, 2013. The cash provided by financing activities for the year ended December 31, 2014 reflects net proceeds of \$112.8 million from the sale of common stock as part of a public offering of our common stock in July 2014, and the proceeds from the exercise of stock options and shares issued under our employee stock purchase plan. The cash provided by financing activities during the year ended December 31, 2013 was driven primarily by proceeds of \$72.4 million from the sale of preferred stock and proceeds of \$113.2 million from our initial public offering.

Net cash provided by financing activities was \$185.9 million during the year ended December 31, 2013 compared to \$9.5 million during the year ended December 31, 2012. The increase in cash provided by financing activities during the year ended December 31, 2013 was driven primarily by proceeds of \$72.4 million from the sale of preferred stock and proceeds of \$113.2 million from our initial public offering.

### **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 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 existing cash, cash equivalents and investments will enable us to fund our current operating plan and capital expenditure requirements into 2018. 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 reviews 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;

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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 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.

**Contractual Obligations**

As of December 31, 2014, we had the following contractual obligations:

<b>Contractual Obligations</b>	<b>Total</b>	<b>Payments Due by Period</b>			
		<b>Less than 1 Year</b>	<b>1 to 3 Years</b>	<b>3 to 5 Years</b>	<b>More than 5 Years</b>
		<b>(in thousands)</b>			
Operating lease obligations(1)	\$ 10,321	\$ 784	\$ 2,750	\$ 2,893	\$ 3,894
Purchase obligations(2)					
<b>Total contractual cash obligations</b>	<b>\$ 10,321</b>	<b>\$ 784</b>	<b>\$ 2,750</b>	<b>\$ 2,893</b>	<b>\$ 3,894</b>

(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. We have not included these payments in the table of contractual obligations above since the contracts are cancelable at any time by us, generally upon 30 days prior written notice to the vendor.

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 royalty payments are probable of occurrence.

*Multiple Myeloma Research Foundation*

In July 2011, we entered into a research agreement with the Multiple Myeloma Research Foundation, or 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.



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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.

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**

In May 2014, the Financial Accounting Standards Board ( FASB ) issued Accounting Standards Update ( ASU ) No. 2014-09, Revenue from Contracts with Customers ( ASU 2014-09 ), which supersedes the revenue recognition requirements in Accounting Standards Codification Topic 605, Revenue Recognition and most industry-specific guidance. The new standard requires that an entity recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the company expects to be entitled in exchange for those goods or services. The update also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. ASU 2014-09 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2016 and should be applied retrospectively to each prior reporting period presented or retrospectively with the cumulative effect of initially applying this update recognized at the date of initial application. We have not yet determined the potential effects of the adoption of this standard on our consolidated financial position, results of operations or cash flows.

On June 10, 2014, the FASB issued ASU 2014-10, which simplifies financial reporting for development stage entities by eliminating requirements specific to development stage entities. As a result, entities in a development stage will no longer need to present inception-to-date information about income statement line items, cash flows, and equity transactions. Instead, the new guidance clarifies how these entities should tailor existing disclosures to explain the risks and uncertainties related to their activities. This update is effective for annual periods beginning after December 15, 2014, and early application is permitted for any annual or interim period for which the entity's financial statements have not yet been issued. We have adopted this guidance prior to issuing the interim financial statements for the three and six months ended June 30, 2014. The adoption of ASU 2014-10 impacted disclosure only and did not have any impact on our financial position or results of operations.



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In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements – Going Concern (Subtopic 205-40): *Disclosure of Uncertainties about an Entity’s Ability to Continue as a Going Concern*. ASU No. 2014-15 is intended to define management’s responsibility to evaluate whether there is substantial doubt about an organization’s ability to continue as a going concern and to provide related footnote disclosures. Substantial doubt about an entity’s ability to continue as a going concern exists when relevant conditions and events, considered in the aggregate, indicate that it is probable that the entity will be unable to meet its obligations as they become due within one year after the date that the financial statements are issued (or available to be issued). ASU No. 2014-15 provides guidance to an organization’s management, with principles and definitions that are intended to reduce diversity in the timing and content of disclosures that are commonly provided by organizations in the financial statement footnotes. ASU No. 2014-15 is effective for annual reporting periods ending after December 15, 2016, and to annual and interim periods thereafter. Early adoption is permitted. We are currently in the process of evaluating the impact of adoption of ASU No. 2014-15 on our consolidated financial statements and related disclosures.

**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, 2014 and 2013, we had cash, cash equivalents, restricted cash and investments of \$214.8 million and \$156.0 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. In addition, we maintain significant amounts of cash, cash equivalents and available-for-sale 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 CROs and CMOs that are located in Canada and Europe, which are 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 reports of our independent registered public accounting firms, appear on pages 100 through 124 of this Annual Report on Form 10-K.

**Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure**

On April 11, 2014, the Audit Committee of the Board of Directors selected Ernst & Young LLP (E&Y) as the Company’s independent registered public accounting firm for the fiscal year ending December 31, 2014, and dismissed McGladrey LLP (McGladrey) from service as the Company’s independent registered public accounting firm. The Company formally engaged E&Y on April 17, 2014. This change in accounting firms was reported in the Company’s



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**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), 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, 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, concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2014.

***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, 2014.

***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, 2014 that have materially affected, or are reasonably likely to materially affect, our internal control over financial

reporting.

**Item 9B. Other Information**

None.

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**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 2015 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2015 Proxy Statement. We expect to file our 2015 Proxy Statement with the SEC no later than April 30, 2015.

**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 2015 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](http://www.karyopharm.com) or request a copy without charge from:

Karyopharm Therapeutics Inc.

Attention: Investor Relations

85 Wells Avenue, 2<sup>nd</sup> 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 2015 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 2015 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 2015 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 2015 Proxy Statement and is incorporated herein by reference.



**Table of Contents****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.

	<b>Page number</b>
<u>Report of Independent Registered Public Accounting Firm</u>	100
<u>Report of Independent Registered Public Accounting Firm</u>	101
<u>Consolidated Balance Sheets as of December 31, 2014 and 2013</u>	102
<u>Consolidated Statements of Operations for the years ended December 31, 2014, 2013 and 2012</u>	103
<u>Consolidated Statements of Comprehensive Loss for the years ended December 31, 2014, 2013 and 2012</u>	104
<u>Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit) for the years ended December 31, 2014, 2013 and 2012</u>	105
<u>Consolidated Statements of Cash Flows for the years ended December 31, 2014, 2013 and 2012</u>	107
<u>Notes to Consolidated Financial Statements</u>	108
<b>(a)(2) Financial Statement Schedules</b>	

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 exhibits and are incorporated herein.

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**Report of Independent Registered Public Accounting Firm**

To the Board of Directors and Stockholders

Karyopharm Therapeutics Inc.

We have audited the accompanying consolidated balance sheet of Karyopharm Therapeutics Inc. (the Company) as of December 31, 2014 and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for the year ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, 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. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the Company's financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of Karyopharm Therapeutics Inc. as of December 31, 2014, and the consolidated results of its operations and its cash flows for the year ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 13, 2015

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**REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

To the Board of Directors and Stockholders

Karyopharm Therapeutics Inc.

We have audited the accompanying consolidated balance sheet of Karyopharm Therapeutics Inc. (the Company) as of December 31, 2013, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the two years in the period then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, 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. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Karyopharm Therapeutics Inc. as of December 31, 2013, and the results of their operations and their cash flows for each of the two years in the period then ended, in conformity with U.S. generally accepted accounting principles.

/s/ McGladrey LLP

Boston, Massachusetts

March 21, 2014

**Table of Contents****Karyopharm Therapeutics Inc.****Consolidated Balance Sheets**

(in thousands, except share and per share amounts)

	<b>December 31, 2014</b>	<b>December 31, 2013</b>
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents	\$ 150,609	\$ 155,974
Short-term investments	55,115	
Prepaid expenses and other current assets	2,027	1,982
Total current assets	207,751	157,956
Property and equipment, net	2,754	240
Long-term investments	8,658	
Other assets	774	30
Restricted cash	400	
Total assets	\$ 220,337	\$ 158,226
<b>LIABILITIES AND STOCKHOLDERS EQUITY</b>		
Current liabilities:		
Accounts payable	\$ 6,288	\$ 1,740
Accrued expenses	5,825	1,168
Deferred revenue		79
Deferred rent	126	
Other current liabilities	62	305
Total current liabilities	12,301	3,292
Deferred rent, net of current portion	1,242	
Total liabilities	13,543	3,292
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; 32,699,380 and 29,587,258 shares issued and outstanding at December 31, 2014 and 2013, respectively	3	3
Additional paid-in capital	345,166	217,500
Accumulated other comprehensive loss	(29)	

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Accumulated deficit	(138,346)	(62,569)
Total stockholders' equity	206,794	154,934
Total liabilities and stockholders' equity	\$ 220,337	\$ 158,226

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

**Table of Contents****Karyopharm Therapeutics Inc.****Consolidated Statements of Operations****(in thousands, except share and per share amounts)**

	<b>For the Years Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Contract and grant revenue	\$ 229	\$ 387	\$ 634
Operating expenses:			
Research and development	60,127	28,452	14,095
General and administrative	15,948	5,885	2,429
Total operating expenses	76,075	34,337	16,524
Loss from operations	(75,846)	(33,950)	(15,890)
Other income (expense):			
Interest income	97	3	2
Interest expense	(1)		
Other expense	(27)		
Total other income (expense), net	69	3	2
Net loss	\$ (75,777)	\$ (33,947)	\$ (15,888)
Net loss per share applicable to common stockholders-basic and diluted	\$ (2.43)	\$ (5.59)	\$ (8.95)
Weighted-average number of common shares outstanding used in net loss per share applicable to common stockholders- basic and diluted	31,135,694	6,067,679	1,775,323

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

**Table of Contents****Karyopharm Therapeutics Inc.  
Consolidated Statements of Comprehensive Loss****(in thousands)**

	<b>For the Years Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Net loss	\$ (75,777)	\$ (33,947)	\$ (15,888)
Other comprehensive income (loss):			
Unrealized loss on investments	(22)		
Foreign currency translation adjustment	(7)		
Comprehensive loss	\$ (75,806)	\$ (33,947)	\$ (15,888)

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

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**Karyopharm Therapeutics Inc.**

**Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)**

(in thousands, except share amounts)

	Series A Convertible Preferred Shares		Series A-2 Convertible Preferred Shares		Series A-3 Convertible Preferred Shares		Series A-4 Convertible Preferred Shares		Series B Convertible Preferred Shares	
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount
	10,937,500	\$ 10,778		\$		\$		\$		\$
	7,500,000	7,500								
	18,437,500	18,278								
	2,500,000	2,500								



23,100,000 46,057

6,100,000 6,980 1,764,706 3,000 1,538,461 2,000 1,000,000 2,000

(20,937,500) (20,778) (6,100,000) (6,980) (1,764,706) (3,000) (1,538,461) (2,000) (24,100,000) (48,057)

\$

\$

\$

\$

\$

\$

Table of Contents**Karyopharm Therapeutics Inc.****Consolidated Statements of Convertible Preferred Stock and Stockholders Equity (Deficit) (Continued)**

(in thousands, except share amounts)

	Preferred Stock Subscription		Common Shares				Total Shareholders Equity (Deficit)	
	Shares	Amount	Shares	Amount	Accumulated Other Comprehensive Loss	Additional Paid-In Capital		Accumulated Deficit
<b>Balance at December 31, 2011</b>	6,100,000	\$ 6,980	1,228,206	\$	\$	\$ 83	\$ (12,734)	\$ (12,651)
Vesting of restricted stock			575,547					
Exercise of stock options			319,635			9		9
Issuance of Series A convertible preferred stock								
Proceeds from the sale of Series A-4 convertible preferred stock	1,538,461	2,000						
Stock-based compensation expense						653		653
Net loss							(15,888)	(15,888)
<b>Balance at December 31, 2012</b>	7,638,461	8,980	2,123,388			745	(28,622)	(27,877)
Issuance of Series A preferred stock								
Proceeds from the sale of Series A-3 convertible preferred stock	1,764,706	3,000						
Proceeds from the sale of Series B convertible preferred stock	1,000,000	2,000						
Issuance of Series B preferred stock, net of issuance costs of \$143								

Issuance of Series B-1 preferred stock, net of issuance costs of \$123					
Issuance of shares related to preferred stock subscription	(10,403,167)	(13,980)			
Conversion of convertible preferred stock into common stock	19,114,241	2	99,689		99,691
Settlement of special participation preferred shares	12,121		88		88
Exercise of stock options	79,122		34		34
Vesting of restricted stock	438,386		5		5
Initial Public Offering, net of issuance costs of \$3,207	7,820,000	1	113,154		113,155
Stock-based compensation expense			3,785		3,785
Net loss				(33,947)	(33,947)
<b>Balance at December 31, 2013</b>	29,587,258	3	217,500	(62,569)	154,934
Vesting of restricted stock	155,058		305		305
Exercise of stock options and shares issued under the employee stock purchase plan	112,730		284		284
Stock-based compensation expense			14,240		14,240
Issuance of common stock upon public offering, net of issuance costs of \$794	2,844,334		112,837		112,837
Unrealized loss on investments			(22)		(22)
Foreign currency translation adjustment			(7)		(7)
Net loss				(75,777)	(75,777)

<b>Balance at December 31, 2014</b>	\$	32,699,380	\$ 3	\$ (29)	\$ 345,166	\$ (138,346)	\$ 206,794
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The accompanying notes are an integral part of these consolidated financial statements.

**Table of Contents****Karyopharm Therapeutics Inc.****Consolidated Statements of Cash Flows****(in thousands)**

	<b>For the Year Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
<b>Operating activities</b>			
Net loss	\$ (75,777)	\$ (33,947)	\$ (15,888)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	323	144	122
Noncash consulting expense		88	
Loss on disposal of fixed assets	50		
Net amortization of premiums and discounts on investments	2		
Stock-based compensation expense	14,240	3,785	653
Change in operating assets and liabilities:			
Prepaid expenses and other current assets	(45)	(1,419)	(209)
Other assets	(470)		
Accounts payable	4,496	664	(66)
Accrued expenses and other liabilities	4,445	382	13
Deferred revenue	(79)	13	(134)
Deferred rent	1,368		
Net cash used in operating activities	(51,447)	(30,290)	(15,509)
<b>Investing activities</b>			
Purchases of property and equipment	(2,834)	(57)	(121)
Increase in restricted cash	(400)		
Purchases of investments	(63,797)		
Net cash used in investing activities	(67,031)	(57)	(121)
<b>Financing activities</b>			
Proceeds from issuance of common stock, net of issuance costs	112,837	113,155	9
Proceeds from the exercise of stock options and shares issued under employee stock purchase plan	284	341	
Proceeds from issuance of preferred stock subscription			2,000
Proceeds from sale of convertible preferred stock, net of issuance costs		72,434	7,500
Net cash provided by financing activities	113,121	185,930	9,509
Effect of exchange rate on cash	(8)		
Net (decrease) increase in cash and cash equivalents	(5,365)	155,583	(6,121)
Cash and cash equivalents, beginning of period	155,974	391	6,512

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Cash and cash equivalents, end of period	\$ 150,609	\$ 155,974	\$ 391
<b>Supplemental disclosure of non-cash investing and financing activities:</b>			
Property and equipment purchases included in accounts payable	\$ 52	\$	\$
Issuance of preferred stock in satisfaction of preferred stock subscription	\$	\$ 13,980	\$
Preferred stock conversion to common stock	\$	\$ 99,691	\$
Vesting of restricted common stock	\$ 305	\$ 5	\$
Deferred financing costs included in accrued expenses	\$ 274	\$	\$

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

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**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 related to its primary business purpose to date and is subject to a number of risks similar to those of other early stage life science companies, including 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 is also subject to a number of risks similar to other companies in the industry, including rapid technological change, regulatory approval of products, uncertainty of market acceptance of products, competition from substitute products and larger companies, the need to obtain additional financing, compliance with government regulations, protection of proprietary technology, dependence on third parties, product liability and dependence on key individuals.

The Company has generated an accumulated deficit of \$138,346 since inception. The Company has financed its operations primarily through private placements of its preferred stock, an initial public offering (IPO) completed in November 2013 and follow-on offerings in July 2014 and January 2015. 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 several years. The Company believes its cash, cash equivalents, and investments as of December 31, 2014 and proceeds from the follow-on offering in January 2015 will be sufficient to allow the Company to fund its current operating plan through at least January 1, 2016.

**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.

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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 revenues and 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, 2014 include the accounts of Karyopharm Therapeutics Inc. (a Delaware corporation), the accounts of Karyopharm Securities Corp. ( "KPSC" , a wholly-owned Massachusetts corporation of the Company incorporated in December 2013), and the accounts of Karyopharm Europe GmbH (a wholly-owned German Limited Liability Company, incorporated in September 2014). At December 31, 2013, the consolidated financial statements also included the accounts of NPM Pharma Inc. ( "NPM" , a wholly-owned Canadian corporation of the Company). As of March 31, 2014, NPM transferred its remaining assets and liabilities to Karyopharm Therapeutics Inc. Following the transfer, NPM was dissolved. The dissolution of NPM had no effect on the consolidated financial statements. All intercompany balances and transactions have been eliminated in consolidation.

### ***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 market value. The Company considers all highly liquid investments with maturities of three months or less from the date of purchase to be 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 comprised 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***

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

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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 comprised 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, 2014 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)
<b>Financial assets</b>				
Money Market Funds, included in cash equivalents	\$ 129,209	\$ 129,209	\$	\$
Investments	63,773		63,773	
	\$ 192,982	\$ 129,209	\$ 63,773	\$

The following table presents information about the Company's financial assets that have been measured at fair value at December 31, 2013 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)
<b>Financial assets</b>				
Money Market Funds, included in cash equivalents	\$ 155,765	\$ 155,765	\$	\$

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### ***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 in accordance with the Financial Accounting Standards Board's (FASB) Accounting Standards Codification (ASC) 605, *Revenue Recognition*. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

persuasive evidence of an arrangement exists;

delivery has occurred or services have been rendered;

the seller's price to the buyer is fixed or determinable; and

collectability is reasonably assured.

The Company recognizes revenue in accordance with the milestone method of revenue recognition for arrangements involving research or development or other performance obligations whereby a portion or all of the consideration is contingent upon achievement of milestone events. Under these provisions, arrangement consideration contingent upon achievement of a milestone is recognized by the Company in the period the milestone is met when the Company concludes that the milestone is substantive. At the inception of each applicable arrangement, the Company assesses

each milestone and the consideration payable upon achievement of each milestone and concludes that the milestone is substantive if all of the following criteria are met: (i) the consideration is commensurate with the Company's performance or the enhanced value of a delivered item which is a direct result of the Company's performance to achieve the milestone, (ii) the consideration relates to past performance and there are no refund rights or other penalties related to the consideration based on completion of future performance and (iii) the consideration is reasonable relative to all the deliverables and payment terms within the arrangement. The related consideration for milestones that are considered substantive is recognized in its entirety in the period which the milestone is met.

The milestone method of revenue recognition was applicable to two research agreements which were executed during 2013 and 2011, respectively.

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The agreement executed during 2013 includes payments upon the achievement of several development milestones as well as an upfront payment. The Company concluded that the upfront payment of \$100 did not represent a substantive milestone. Accordingly, the Company is recognizing this amount on a straight-line basis from the date when substantive services commenced through the estimated completion of the final milestone. During the year ended December 31, 2013 the Company recognized \$21 of the upfront payment and no additional milestones were met according to this research agreement. During the year ended December 31, 2014, the Company recognized \$229 related to this agreement, including \$79 of the upfront payment and \$150 related to other milestones associated with the agreement. The Company could earn additional milestones of up to \$250 under this agreement.

The agreement executed during 2011 includes payments upon the achievement of several development milestones as well as an upfront payment. The Company concluded that the upfront payment of \$200 did not represent a substantive milestone. Accordingly, the Company recognized this amount on a straight-line basis from the date when substantive services commenced through the estimated completion of the final milestone. During the year ended December 31, 2012, the Company recognized \$634 related to this research agreement, including \$134 of the upfront payment. During the year ended December 31, 2013, the Company recognized \$366 related to this agreement, including \$66 related to the upfront payment and \$300 related to other milestones associated with the agreement. There are no future milestones to be met under this agreement. The Company did not recognize revenue under this agreement during the year ended December 31, 2014.

## ***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 conduct clinical trials and preclinical studies;

the cost of acquiring, developing and manufacturing clinical trial materials;

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 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 losses of \$27 were recorded in other expense for the year ended December 31, 2014. There were no foreign exchange gain or loss for the years ended December 31, 2013 and 2012.

**Table of Contents*****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.

***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 and restricted stock and modifications to existing stock options, 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.

***Net Loss Per Share***

Basic and diluted net loss per common share is calculated by dividing net loss applicable to common stockholders by the weighted-average number of common shares outstanding for the period, without consideration for common stock equivalents. The Company's potential dilutive shares, which include convertible preferred stock, special participation stock, outstanding stock options and unvested restricted stock 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, 2014, 2013 and 2012 (in common stock equivalent shares):

	<b>December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Convertible preferred stock			5,587,121
Special participation stock			10,000
Outstanding stock options	3,012,923	2,410,522	691,367
Unvested restricted stock	11,410	166,949	541,218

***Recently Issued Accounting Pronouncements***

In May 2014, the FASB issued Accounting Standards Update ( ASU ) No. 2014-09, *Revenue from Contracts with Customers* ( ASU 2014-09 ), which supersedes the revenue recognition requirements in

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Accounting Standards Codification Topic 605, Revenue Recognition and most industry-specific guidance. The new standard requires that an entity recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the company expects to be entitled in exchange for those goods or services. The update also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. ASU 2014-09 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2016 and should be applied retrospectively to each prior reporting period presented or retrospectively with the cumulative effect of initially applying this update recognized at the date of initial application. The Company has not yet determined the potential effects of the adoption of this standard on its consolidated financial position, results of operations or cash flows.

On June 10, 2014, the FASB issued ASU 2014-10, which simplifies financial reporting for development stage entities by eliminating requirements specific to development stage entities. As a result, entities in a development stage will no longer need to present inception-to-date information about income statement line items, cash flows, and equity transactions. Instead, the new guidance clarifies how these entities should tailor existing disclosures to explain the risks and uncertainties related to their activities. This update is effective for annual periods beginning after December 15, 2014, and early application is permitted for any annual or interim period for which the entity's financial statements have not yet been issued. The Company adopted this guidance prior to issuing the interim financial statements for the three and six months ended June 30, 2014. The adoption of ASU 2014-10 impacted disclosure only and did not have any impact on the Company's financial position or results of operations.

In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40): *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*. ASU No. 2014-15 is intended to define management's responsibility to evaluate whether there is substantial doubt about an organization's ability to continue as a going concern and to provide related footnote disclosures. Substantial doubt about an entity's ability to continue as a going concern exists when relevant conditions and events, considered in the aggregate, indicate that it is probable that the entity will be unable to meet its obligations as they become due within one year after the date that the financial statements are issued (or available to be issued). ASU No. 2014-15 provides guidance to an organization's management, with principles and definitions that are intended to reduce diversity in the timing and content of disclosures that are commonly provided by organizations in the financial statement footnotes. ASU No. 2014-15 is effective for annual reporting periods ending after December 15, 2016, and to annual and interim periods thereafter. Early adoption is permitted. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2014-15 on its consolidated financial statements and related disclosures.

**3. Property and Equipment, net**

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

		<b>December 31,</b>	
	<b>Estimated Useful</b>	<b>2014</b>	<b>2013</b>
	<b>Life Years</b>		
Laboratory equipment	4	\$ 434	\$ 328
Furniture and fixtures	5	95	98
Office and computer equipment	3	170	85
Construction in progress		92	
Leasehold improvements	Lesser of useful life or lease term	2,457	79

	3,248	590
Less accumulated depreciation and amortization	(494)	(350)
	\$ 2,754	\$ 240

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Depreciation and amortization expense recorded for the years ended December 31, 2014, 2013, and 2012 were \$323, \$144, and \$122, respectively.

**4. Investments**

The following table summarizes the Company's short and long-term investments as of December 31, 2014 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Certificates of deposit	\$ 15,000	\$	\$	\$ 15,000
Corporate debt securities	15,266	2	(20)	15,248
Commercial paper	29,980			29,980
U.S. government and agency securities	3,549	1	(5)	3,545
	\$ 63,795	\$ 3	\$ (25)	\$ 63,773

The fair value of the investments at December 31, 2014 by contractual maturity, are shown below (in thousands):

Due in one year or less	\$ 55,115
Due after one year through two years	8,658
	\$ 63,773

At December 31, 2014, the Company held 11 debt securities that were in an unrealized loss position for less than one year. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2014 was \$12,635. 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, 2014. The Company evaluated its securities for other-than-temporary impairment and considered the decline in market value for the securities to be primarily attributable to current economic and market conditions. It is not more likely than not that the Company will be required to sell the securities, and the Company does not intend to do so prior to the recovery of the amortized cost basis. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of December 31, 2014.

**5. Accrued Liabilities**

Accrued expenses consist of the following (in thousands):

	December 31, 2014	2013
Research and development costs	3,624	\$ 698

Payroll and employee-related costs	1,568	100
Professional fees	324	215
Other	309	155
	\$ 5,825	\$ 1,168

## 6. Related Party Transactions

The Company incurred expenses for consulting and contract research services with certain related parties, including a family member of management and a board member, of \$512, \$418, and \$109, for the years ended December 31, 2014, 2013, and 2012. At December 31, 2014, there was \$88 included in accounts payable and accrued expenses due to related parties. There are no amounts included in accounts payable or accrued expenses at December 31, 2013 due to related parties.

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**7. Stockholders Equity**

***Common Stock***

In July 2014, the Company completed a public offering of its common stock, which resulted in the sale of 2,447,247 shares of its common stock at a public offering price of \$42.50 per share. Also, in July 2014, the Company issued 397,087 shares of its common stock upon exercise by the underwriters of their option to purchase additional shares. The Company received net proceeds of approximately \$112,837, after deducting underwriting discounts, commissions and expenses payable by the Company of \$794.

In November 2013, the Company closed an IPO of its common stock, which resulted in the sale of 6,800,000 shares of its common stock at a public offering price of \$16.00 per share. In December 2013, the Company issued 1,020,000 shares of common stock upon the exercise by the underwriters of their option to purchase additional shares at the public offering price. The Company received net proceeds from the IPO of approximately \$113,155, after deducting underwriting discounts and expenses payable by the Company.

In connection with preparing for the IPO, the Company's Board of Directors and stockholders approved a one-for-3.3 reverse stock split of the Company's common stock. The reverse stock split became effective in October 2013. All share and per share amounts in the consolidated financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital.

In connection with the closing of the IPO, all of the Company's outstanding convertible preferred stock automatically converted to common stock in November 2013, resulting in an additional 19,114,241 shares of common stock of the Company becoming outstanding. The significant increase in common stock outstanding in November 2013 is expected to impact the year-over-year comparability of the Company's net loss per share calculations in future periods. Upon the closing of its IPO, the Company had 5,000,000 shares of authorized preferred stock. As of December 31, 2014 and 2013, the Company does not have any preferred stock issued or outstanding.

In October 2010, the Company issued and sold 1,958,210 shares of its common stock, subject to restrictions that vest over time, to the founders of the Company for an aggregate cash consideration of \$1. In October 2010, the Company entered into a service contract and, pursuant to the terms of such contract, the Company was obligated to issue shares. The Company issued 162,685 shares of common stock in connection with this service contract. In December 2011, the Company issued and sold 45,454 shares of its common stock, subject to restrictions that vest over time, to two advisors of the Company for an aggregate cash consideration of \$12. In accordance with the terms of the restricted stock agreements, the Company has the right (but not an obligation) to repurchase, at the original purchase price, any unvested shares of the restricted common stock in the event of termination of the business relationship. Restricted shares are recorded as outstanding as they vest. There were 11,410 and 166,949 shares of unvested restricted common stock at December 31, 2014 and December 31, 2013, respectively.

In October of 2010, the Company entered into an agreement to issue and sell 20,000,000 shares of Series A Preferred Stock at \$1.00 per share, which was effectuated in two tranches. The first closing of the first tranche occurred in October 2010, in which the Company issued and sold 5,000,000 shares of Series A Preferred Stock for gross proceeds of \$5,000. The remaining 5,000,000 shares of the first tranche were issued and sold in 2011 for gross proceeds of \$5,000. In accordance with the terms of the Series A Preferred Stock Purchase Agreement, the Company issued and sold an additional 10,000,000 shares of Series A Preferred Stock in the second tranche, of which 2,500,000 shares were sold upon the achievement of a pre-defined milestone, and 2,500,000 shares were sold in each of the following three calendar quarters, for total cash consideration of \$10,000. As discussed below, the Company met this milestone



in June 2012.

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On October 31, 2011, the Company entered into a stock purchase agreement with an existing stockholder for the purpose of issuing and selling up to 7,000,000 shares of Series A-2 Preferred Stock and the sale of up to 3,000,000 shares of Series A-3 Preferred Stock in two closings.

Pursuant to this agreement, the Company agreed to sell 6,100,000 shares of Series A-2 Preferred Stock at \$1.15 per share for gross proceeds of \$6,980. The Company accounted for this stock purchase as a preferred stock subscription as these shares were not issued until August 2013.

Upon meeting a pre-defined clinical milestone in February 2013, the Company agreed to sell 1,764,706 shares of Series A-3 Preferred Stock at \$1.70 per share for gross proceeds of \$3,000. The Company accounted for this stock purchase as a preferred stock subscription as these shares were not issued until August 2013.

In February 2012, the Company agreed to sell 1,538,461 shares of Series A-4 Preferred Stock at \$1.30 per share for gross proceeds of \$2,000. The Company accounted for this stock purchase as a preferred stock subscription as these shares were not issued until August 2013.

In June 2012, the Company achieved the milestone for the second tranche of the Series A Preferred Stock Agreement. In accordance with the terms of the Agreement, the Company sold 2,500,000 shares of Series A Preferred Stock in June 2012 for \$2,500 and sold 2,500,000 shares of Series A Preferred Stock in each of the following three calendar quarters.

Between April and July 2013, the Company issued and sold an aggregate of 11,600,000 shares of Series B Preferred Stock at a price per share of \$2.00 for an aggregate purchase price of \$23,200. Upon the earlier of (i) September 6, 2013 or (ii) immediately prior to the closing of a firm commitment underwritten initial public offering of the Company's securities pursuant to an effective registration statement filed with the SEC, certain of the Company's existing investors were obligated to purchase an additional 12,500,000 shares of the Company's Series B Preferred Stock at a price per share of \$2.00, for gross proceeds of \$25,000. Such shares were issued in September 2013.

In July 2013, the Company issued and sold an aggregate of 8,636,362 shares of Series B-1 Preferred Stock at a price per share of \$2.20 for gross proceeds of \$19,000.

In August 2013, the Company issued (i) an aggregate of 6,100,000 shares of its series A-2 preferred stock at a purchase price per share of \$1.15, for an aggregate purchase price of \$7,015, (ii) an aggregate of 1,764,706 shares of its series A-3 preferred stock at a purchase price per share of \$1.70, for an aggregate purchase price of \$3,000, and (iii) an aggregate of 1,538,461 shares of its series A-4 preferred stock, at a purchase price per share of \$1.30, for an aggregate purchase price of \$2,000.

The Company has evaluated the tranching nature of certain of its Preferred Stock financings, as well as its rights, preferences and privileges of each series of Preferred Stock and has concluded that there are no freestanding derivative instruments, embedded derivatives requiring bifurcation, or any beneficial conversion features. All issued and subscribed shares of Preferred Stock were classified outside of Stockholders' Equity (Deficit) prior to their conversion to shares of common stock due to the presence of deemed liquidation provisions in the underlying agreements.

### ***Special Participation Stock***

Upon the sale of Series A Preferred Stock, the Company amended various restricted stock agreements to allow for the sale and issuance of 10,000 shares of special participation stock ( *Special Participation Stock* ) for \$0.0001 per share

(par value) for nominal consideration. The fair value of these shares during 2011 and 2012 was immaterial. In accordance with the terms of the amended restricted stock agreements, the Company has the right (but not an obligation) to repurchase, at the original purchase price, any unvested shares of Special Participation Stock in the event of termination of the underlying business relationship.

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In July 2013, the Company issued 12,121 shares of common stock in settlement of all outstanding shares of Special Participation Stock. There are no outstanding shares of Special Participation Stock at December 31, 2014 and 2013.

**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 provides for the expansion of the premises leased by the Company by approximately 16,234 square feet, and provides the Company with the rights of first offer to lease approximately 27,701 square feet of additional space. 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, 2014, accordingly. The lease provides the Company with an allowance for improvements of \$1,616 of which \$1,048 was incurred through December 31, 2014, was deemed normal tenant improvements and recorded as a leasehold improvement and deferred rent, and will be 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 may be 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 starting February 2015 through January 2020. Pursuant to the lease agreement, the Company is obligated to make aggregate rent payments of 374, (approximately \$455) 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, 2014, the minimum future rent payments under the lease agreements are as follows (in thousands):

2015	\$ 784
2016	1,338
2017	1,412
2018	1,435
2019	1,458
Thereafter	3,894
<b>Total future minimum lease payments</b>	<b>\$ 10,321</b>

The Company recorded rent expense totaling \$520, \$174, and \$127 for the years ended December 31, 2014, 2013, and 2012, 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, up to a predetermined maximum. The Company must also pay a royalty on any sublicense income, up to a predetermined maximum. No royalties or sublicense payments have been made to date.

**Table of Contents*****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 litigation and, accordingly, does not have amounts recorded for any litigation-related matters.

**9. Stock-based Compensation**

During 2010, the Company established the 2010 Stock Incentive Plan (the Plan or the 2010 Plan). As of December 31, 2014, the Company can issue a maximum of 1,693,216 shares under the Plan pursuant to outstanding stock options. Under the terms of the Plan, options and other equity interests may be granted to employees, officers, directors, consultants and advisors of the Company. The exercise price of each stock option shall be 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 has granted service-based options under the Plan. Service-based option grants under the Plan 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 thereafter. The options granted under the Plan generally expire in 10 years.

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, and (C) an amount determined by the Board. The Company will grant no further stock options or other awards under the 2010 Plan.

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

	<b>Year Ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Research and development	\$ 7,078	\$ 2,567	\$ 605
General and administrative	7,162	1,218	48
<b>Total</b>	<b>\$ 14,240</b>	<b>\$ 3,785</b>	<b>\$ 653</b>

***Stock Options***

Total expense related to employee and non-employee stock options for the years ended December 31, 2014, 2013 and 2012 was \$13,962, \$3,020, and \$264, respectively.



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

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Options outstanding at December 31, 2013	2,410,522	\$ 7.85	9.3	\$ 36,717
Granted	900,200	39.18		
Exercised	(106,528)	1.35		
Forfeited	(191,271)	20.27		
Options outstanding at December 31, 2014	3,012,923	\$ 16.65	8.7	\$ 64,659
Options vested or expected to vest at December 31, 2014(1)	2,833,435	\$ 16.48	8.6	\$ 61,271
Options exercisable at December 31, 2014	896,017	\$ 5.53	7.8	\$ 28,591

- (1) This represents the number of vested options, plus the number of unvested options that the Company estimated would vest, based on the unvested options as of the year ended December 31, 2014 as adjusted for the estimated forfeiture rate.

The total intrinsic value of stock options exercised for the years ended December 31, 2014, 2013 and 2012 was \$3,716, \$239, and \$115, 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,		
	2014	2013	2012
Volatility	84%-95%	85%-93%	79%-92%
Expected term (in years)	5.5-9.9	6.25-10	6.25-10
Risk-free interest rate	1.73%-2.15%	1.07%-3.01%	0.85%-1.76%
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. Management estimates expected forfeitures based on data from a representative group of companies with similar characteristics to the Company and recognizes 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, 2014, 2013 and 2012 was \$29.71, \$11.09, and \$1.19 per share, respectively.

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At December 31, 2014, the total unrecognized compensation related to unvested employee and non-employee stock option awards granted under the 2010 Plan and 2013 Plan, including estimated forfeitures, was \$32,671, which the Company expects to recognize over a weighted-average period of approximately 3.2 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 following table summarizes the status of the Company's unvested restricted common shares:

	<b>Number of Shares</b>	<b>Weighted-Average Grant Date Fair Value</b>
Unvested at December 31, 2013	9,943	\$ 0.26
Granted		
Cancelled		
Vested	(5,681)	\$ 0.26
Unvested at December 31, 2014 (1)	4,262	\$ 0.26

(1) Excludes 7,148 shares of unvested restricted stock remaining from the early exercise of stock options as of December 31, 2014.

The total expense related to employee and non-employee restricted stock for the years ended December 31, 2014, 2013 and 2012 was \$193, \$765 and \$389, respectively.

As of December 31, 2014, there was \$158 of total unrecognized compensation cost related to employee and non-employee unvested restricted stock. The unrecognized expense is expected to be recognized over a weighted average period of 0.7 years.

In 2014 certain individuals changed status from employees to non-employees. The outstanding stock option awards for these individuals continued to vest under the original vesting terms of the awards as the individuals continued to provide service to the Company as consultants. In addition, in August 2014, the Company modified a stock option grant for one of these individuals to accelerate vesting of a stock option award in connection with a separation agreement. The Company recorded stock-based compensation expense of \$1,866 associated with these awards. As of December 31, 2014, there was no unrecognized compensation expense related to these awards as the individuals are no longer providing service to the Company.

**Employee Stock Purchase Plan**

The Company has an Employee Stock Purchase Plan ( ESPP ) that permits eligible employees to enroll in a twelve-month offering period comprising two six-month purchase 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 day of the applicable six-month offering period, or the last day of the applicable six-month purchase period, whichever is lower. Purchase dates under the ESPP occur on or about May 1 and November 1 of 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.

During the year ended December 31, 2014, \$141 was withheld from employees, on an after-tax basis, in order to purchase 6,202 shares of the Company's Common Stock. For the year ended December 31, 2014, the Company recorded stock-based compensation expense of \$85. As of December 31, 2014, 236,222 shares of Company's Common Stock remain available for issuance under the ESPP. As of December 31, 2014, there was \$52 of total unrecognized stock-based compensation expense related to the ESPP. The expense is expected to be recognized over a period of four months.

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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:

	<b>Year Ended December 31, 2014</b>
Volatility	75%
Expected term (in years)	0.5
Risk-free interest rate	0.05%
Dividend	0.0%

**10. 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 \$197, \$91 and \$49 to the 401(k) Plan for the years ended December 31, 2014, 2013 and 2012, respectively.

**11. Income Taxes**

The Company provides for income taxes under ASC Topic 740, *Accounting for Income Taxes*. Under ASC Topic 740, the liability method is used in accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities, and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse.

For the years ended December 31, 2014 and 2013, the Company did not record a current or deferred income tax expense or benefit.

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

	<b>Year ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Foreign	\$ (2,887)	\$ (10,922)	\$
U.S.	(72,890)	(23,025)	(15,888)
<b>Totals</b>	<b>\$ (75,777)</b>	<b>\$ (33,947)</b>	<b>\$ 15,888</b>

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:

	<b>Year ended</b>	
	<b>December 31,</b>	
	<b>2014</b>	<b>2013</b>
Deferred tax assets:		
U.S. and state net operating loss carryforwards	\$ 39,970	\$ 17,876
Foreign net operating loss carryforwards		2,731
Stock-based compensation	6,405	
Accruals and other temporary differences	1,225	1,819
Research and development credits	4,161	2,670
Capitalized research and development	4,505	
Total deferred tax assets	56,266	25,096
Less valuation allowance	(56,266)	(25,096)
Net deferred tax assets	\$	\$

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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 its deferred tax assets as of December 31, 2014 and 2013. The valuation allowance increased by approximately \$31.2 million and \$13.3 million during the years ended December 31, 2014 and 2013, respectively, due primarily to the generation of net operating losses during the periods then ended.

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:

	<b>Year ended December 31,</b>		
	<b>2014</b>	<b>2013</b>	<b>2012</b>
Federal income tax expense at statutory rate	34.0%	34.0%	34.0%
State income tax, net of federal benefit	4.9%	4.9%	5.2%
Permanent differences	(0.7)%	0.0%	(0.1)%
Research and development credit	1.4%	3.9%	0.0%
Foreign rate differential	(1.3)%	(2.9)%	0.0%
Other	2.8%	(0.8)%	(0.0)%
Change in valuation allowance	(41.1)%	(39.1)%	(39.1)%
Effective income tax rate	0.0%	0.0%	0.0%

As of December 31, 2014 and 2013, the Company had U.S. federal net operating loss carryforwards of approximately \$105.6 million and \$45.5 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2034. As of December 31, 2014 and 2013, the Company also had U.S. state net operating loss carryforwards of approximately \$104.4 million and \$45.9 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2034. Included in the U.S. federal and state net operating loss carryforwards is a deduction for option exercises of \$3.8 million and \$0.2 million as of December 31, 2014 and 2013, respectively.

As of December 31, 2014, the Company had liquidated its Canadian subsidiary resulting in the loss of its net operating loss carryforwards there.

As of December 31, 2014 and 2013, the Company had federal research and development tax credit carryforwards of approximately \$3.0 million and \$2.0 million, respectively, available to reduce future tax liabilities which expire at various dates through 2034. As of December 31, 2014 and 2013, the Company had state research and development tax credit carryforwards of approximately \$1.7 million and \$1.0 million, respectively, available to reduce future tax liabilities which expire at various dates through 2029.

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 may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

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The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2014 and 2013, 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.

For all years through December 31, 2014, the Company generated research and development 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 for these two years. 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.

The Company and one of its subsidiaries file income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2011 through December 31, 2014. 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.

**12. Subsequent Events**

In January 2015, the Company completed an underwritten offering of 2,950,000 shares of the Company's common stock, par value \$0.0001 per share, at a price of \$33.00 per share, less the underwriting discount. The net proceeds received by the Company were approximately \$90,868 after deducting the underwriting discount and estimated offering expenses payable by the Company.

**13. Selected Quarterly Financial Information (Unaudited)**

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

	<b>First Quarter</b>	<b>Second Quarter</b>	<b>Third Quarter</b>	<b>Fourth Quarter</b>
<b>Year Ended December 31, 2014</b>				
Contract and grant revenue	\$ 171	\$ 21	\$ 21	\$ 16
Total operating expenses	\$ 13,883	\$ 16,469	\$ 19,765	\$ 25,958
Loss from operations	\$(13,712)	\$(16,448)	\$(19,744)	\$(25,942)
Total other income (expense)	\$ 18	\$ 17	\$ 20	\$ 14
Net loss	\$(13,694)	\$(16,431)	\$(19,724)	\$(25,928)
Net loss per share applicable to common stockholders, basic and diluted	\$ (0.46)	\$ (0.55)	\$ (0.61)	\$ (0.79)
	<b>First Quarter</b>	<b>Second Quarter</b>	<b>Third Quarter</b>	<b>Fourth Quarter</b>
<b>Year Ended December 31, 2013</b>				
Contract and grant revenue	\$ 233	\$ 133	\$ 21	\$ 21
Total operating expenses	\$ 5,844	\$ 7,003	\$ 9,321	\$ 12,169
Loss from operations	\$(5,611)	\$(6,870)	\$(9,321)	\$(12,148)
Total other income (expense)	\$	\$ 1	\$	\$ 2
Net loss	\$(5,611)	\$(6,869)	\$(9,321)	\$(12,146)



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Net loss per share applicable to common  
stockholders, basic and diluted

\$ (2.52)    \$ (2.86)    \$ (3.66)    \$ (0.72)

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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 13, 2015

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.

<b>Signature</b>	<b>Title</b>	<b>Date</b>
/s/ Michael G. Kauffman Michael G. Kauffman, M.D., Ph.D.	Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	March 13, 2015
/s/ Justin A. Renz	Executive Vice President & Chief Financial Officer	March 13, 2015
Justin A. Renz	<i>(Principal Financial and Accounting Officer)</i>	
/s/ Garen G. Bohlin Garen G. Bohlin	Director	March 13, 2015
/s/ J. Scott Garland J. Scott Garland	Director	March 13, 2015
/s/ Barry E. Greene Barry E. Greene	Director	March 13, 2015
/s/ Deepa R. Pakianathan Deepa R. Pakianathan, Ph.D.	Director	March 13, 2015
/s/ Mansoor Raza Mirza Mansoor Raza Mirza, M.D.	Director	March 13, 2015
/s/ Kenneth E. Weg Kenneth E. Weg	Director	March 13, 2015

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<b>Exhibit Number</b>	<b>Description of Exhibit</b>
	<i>Articles of Incorporation and Bylaws</i>
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)
	<i>Instruments Defining the Rights of Security Holders, Including Indentures</i>
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)
	<i>Material Contracts Management Contracts and Compensatory Plans</i>
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	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)
10.7	

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Employment Agreement dated December 6, 2010 between the Registrant and Michael Kauffman, M.D., Ph.D. (incorporated by reference to Exhibit 10.7 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed on October 28, 2013)

10.8

Employment Agreement dated October 19, 2010, as amended on December 6, 2010, between the Registrant and Sharon Shacham, Ph.D., M.B.A. (incorporated by reference to Exhibit 10.8 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed on October 28, 2013)

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<b>Exhibit Number</b>	<b>Description of Exhibit</b>
10.9	Employment Agreement dated May 29, 2013 between the Registrant and Paul Brannelly (Incorporated by reference to Exhibit 10.9 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)
10.10	Consulting Agreement, dated as of September 1, 2012, between the Registrant and Mirza Consulting (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
10.11	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)
10.12	Offer Letter from the Registrant to Christopher Primiano dated March 3, 2014 (incorporated by reference to Exhibit 10.13 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 21, 2014)
10.13	Offer letter, dated July 7, 2014, between the Registrant and Justin Renz (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed on August 8, 2014)
10.14	Consulting Agreement, dated August 7, 2014, between the Registrant and Paul Brannelly (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 8, 2014)
10.15	Separation Agreement, dated August 7, 2014, between the Registrant and Paul Brannelly (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 8, 2014)
10.16	Managing Director Agreement, dated October 15, 2014, by and between Karyopharm Europe GmbH and Ran Frenkel
10.17	Letter Agreement, dated October 15, 2014, by and between Karyopharm Therapeutics Inc. and Ran Frenkel.
10.18	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)
10.19	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)
10.20	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)
10.21	Amended and Restated Letter Agreement, dated as of January 23, 2015, between the Registrant and Christopher Primiano
10.22	

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Amendment to Managing Director Agreement, dated February 15, 2015, by and between Karyopharm Europe GmbH and Ran Frenkel

***Material Contracts Leases***

10.23

Lease, dated as of December 10, 2010, as amended on January 10, 2012 and July 29, 2013, between the Registrant and Nivek Investments I, LLC (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)

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<b>Exhibit Number</b>	<b>Description of Exhibit</b>
10.24	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)
10.25	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)
	<b><i>Material Contracts Research Agreements</i></b>
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)
	<b><i>Additional Exhibits</i></b>
16.1	Letter from McGladrey LLP to the Commission, dated April 17, 2014 (incorporated by reference to Exhibit 16.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on April 17, 2014)
21.1	Subsidiaries of the Registrant
23.1	Consent of Ernst & Young LLP (Independent registered public accounting firm for the Company)
23.2	Consent of McGladrey 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 and Chief Financial 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
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 Justin A. Renz, Executive Vice President and Chief Financial Officer of the Registrant
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.