Karyopharm Therapeutics Inc.
Form 10-K
March 21, 2014

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2013

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

For the transition period from to
Commission file number: 001-36167

KARYOPHARM THERAPEUTICS INC.

(Exact name of registrant as specified in its charter)

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

2 Mercer Road, Natick, Massachusetts 01760
(Address of principal executive offices) (zip code)
Registrant's telephone number, including area code: **(508) 975-4820**

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

(Title of each class)	**(Name of each exchange on which listed)**

Common Stock, $0.0001 par value	NASDAQ Global Select Market

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

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

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 o No ý

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 ý No o

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 ý No o

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. o

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 o	Accelerated filer o	Non-accelerated filer ý (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No ý

The aggregate market value of voting stock held by non-affiliates of the registrant on November 6, 2013 (including shares issued in the registrant's initial public offering), based on the closing price of $16.05 for shares of the registrant's common stock as reported by the NASDAQ Global Select Market, was approximately $198,461,380. The registrant has elected to use November 6, 2013 as the calculation date, which was the initial trading date of the registrant's common stock on the NASDAQ Global Select Market, because on June 30, 2013 (the last business day of the registrant's most recently completed second fiscal quarter), the registrant was a privately-held company. 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 14, 2014: 29,753,726.

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2014 in connection with our 2014 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 2014, 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 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 wholly-owned, novel, small molecule, **Selective Inhibitors of Nuclear Export,** or **SINE**, compounds that inhibit the nuclear export protein XPO1. 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 240 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 8-12 months. We plan to initiate three clinical trials during 2014 designed to potentially serve as the basis for an application seeking regulatory approval for Selinexor in hematological malignancy indications. To our knowledge, no other XPO1 inhibitors are in clinical development at the present time.

The nucleus contains a cell's genetic material, or DNA, and acts as the control center of the cell, while the cytoplasm is the intracellular compartment around the nucleus where numerous processes involving proteins and other molecules 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. 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 occur. There are seven known nuclear export proteins (Exportins 1 through 7), of which the most well-characterized is Exportin 1, or XPO1, also known as CRM1. XPO1 mediates the export of approximately 220 different mammalian cargo proteins, including the vast majority of tumor suppressor

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proteins. Moreover, XPO1 appears to be the only nuclear exporter for most of these tumor suppressor proteins. Tumor suppressor proteins are anti-cancer proteins which must be in the nucleus to carry out their main function of detecting damage to genetic material that may indicate cancer, and, subsequently, initiating programmed cell death, or apoptosis, of the damaged cells. Cancer cells have increased levels of XPO1, causing the increased export of these tumor suppressor proteins from the nucleus, and thus counteracting 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. The accumulation of tumor suppressor proteins in the nucleus reinitiates and amplifies their natural apoptotic function in cancer cells. This leads to the death of cancer cells through apoptosis with minimal effects on normal cells.

We are focused on building a leading oncology business. We were founded in December 2008 by Dr. Sharon Shacham, who established the Company to focus on the discovery and development of small molecule inhibitors of nuclear export. Dr. Shacham has led our company since its inception, and now serves as our President and Chief Scientific Officer, and co-chair of our Scientific Advisory Board. Her computational drug discovery algorithms formed a critical part of the technological basis for our drug discovery and optimization platform, which was used for the discovery of Selinexor, our lead drug candidate. 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. Along with Dr. Shacham, we are led by Dr. Michael Kauffman, M.D., Ph.D., who joined the Company in January 2011 and now serves as our Chief Executive Officer. Dr. Kauffman played a leadership role in the development and approval of Velcade® at Millenium Pharmaceuticals, and of Kyprolis® while serving as Chief Medical Officer at Proteolix and then Onyx Pharmaceuticals.

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 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.

We are currently conducting three open-label Phase 1 clinical trials of Selinexor, 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 preliminary 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. Assuming continued positive results from our ongoing Phase 1 clinical trials of Selinexor and pending regulatory feedback, we plan to initiate registration-directed clinical trials of Selinexor in three hematological malignancy indications during 2014. We refer to these trials as registration-directed because they are designed to potentially serve as the basis for an application seeking regulatory approval of Selinexor. We expect to initiate registration-directed clinical trials for Selinexor in acute myeloid leukemia, or AML, in the first half of 2014, in diffuse large B-cell lymphoma, or DLBCL, in late summer 2014 and in Richter's Syndrome during the middle of 2014. We plan to seek regulatory approvals of Selinexor in North America and Europe in each such indication with respect to which we receive positive clinical trial

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results and positive regulatory feedback. We may seek such approvals in other geographies as well. In solid tumor malignancies, we have initiated Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014. As we continue to review response data in solid tumor and other hematological malignancies, including multiple myeloma, we may decide to initiate registration-directed trials in additional cancer indications. We intend to enter into collaborations for marketing and commercialization of Selinexor in particular geographies at an appropriate time.

We designed our Phase 1 clinical trials of Selinexor in relapsed and/or refractory hematological malignancies and relapsed and/or refractory solid tumor malignancies to evaluate the safety of Selinexor, to determine the Phase 2 clinical trial dose and dosing schedule and to evaluate preliminary anti-cancer activity of Selinexor. In patients evaluated in our hematological malignancy trial as of December 4, 2013, we have observed complete responses or remissions, partial responses or remissions, minimal responses or stable disease, all as determined in accordance with commonly accepted evaluation criteria for the specific indication. For example, partial or minimal responses or stable disease have been observed in 82% of patients with relapsed and/or refractory chronic B-cell malignancies. In patients with relapsed and/or refractory acute myeloid leukemia, we have observed complete remissions, partial remission, morphologic leukemia-free state or stable disease in 52% of patients, some for longer than three months. In 48% of patients in the solid tumor malignancy trial evaluated as of December 24, 2013, we have observed partial responses or stable disease, all as determined in accordance with Response Evaluation Criteria In Solid Tumors, or RECIST.

In addition to cancer, we believe that our SINE compounds have the potential to provide therapeutic benefit in a number of additional indications, including autoimmune and inflammatory diseases, wound healing, HIV and influenza. 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. We may seek to enter into development, marketing and commercialization collaboration arrangements for our SINE compounds other than Selinexor in non-oncology indications globally.

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The table below summarizes the current stages of development of our key drug candidates and indications for which clinical trials are currently being conducted or indications that we expect to initially focus on for each candidate. We expect to initiate the planned clinical trials of Selinexor described below assuming continued positive results from our ongoing Phase 1 clinical trials and pending regulatory feedback. We also expect a number of investigator-sponsored trials, or ISTs, to be initiated for Selinexor in a variety of cancer indications in 2014. These ISTs could consist of single agent or combination studies with other agents in both hematological and solid tumor malignancies.

In addition, we conducted a Phase 2b clinical trial of Verdinexor (KPT-335), a SINE compound that is closely-related to Selinexor, in pet dogs with newly-diagnosed or first relapse after chemotherapy lymphomas. Our Phase 2b clinical trial is intended to support regulatory approval under the MUMS designation. We submitted the safety and effectiveness sections of a New Animal Drug Application to the U.S. Food and Drug Administration for regulatory approval in such indication in December 2013 and, if we obtain such approval, we plan to seek to enter into a collaboration with respect to the commercialization of Verdinexor.

The development of Selinexor, and our other drug candidates, including our other SINE compounds and PAK4 inhibitors, as well as Verdinexor, began with our proprietary drug discovery and optimization platform. We intend to continue using this platform, which includes expertise in computational chemistry, our proprietary virtual chemical library and *in silico* screening know- how, certain biochemical assays and *in silico* complexes of the structures of the target proteins bound with our small molecules, and other trade secrets and know-how, for the discovery and optimization of additional drug candidates for cancer and other major diseases.

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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 Europe. Assuming continued positive results from our ongoing Phase 1 and Phase 2 clinical trials of Selinexor and pending regulatory feedback, we plan to initiate registration-directed clinical trials of Selinexor in three hematological malignancy indications during 2014. We expect to initiate these clinical trials for Selinexor in AML, DLBCL and Richter's Syndrome. We plan to seek regulatory approvals of Selinexor in North America and Europe in each such indication 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 Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014.

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 Europe. As we further develop Selinexor for oncology indications, we intend to evaluate marketing and commercialization opportunities. 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.

Develop Novel Drug Candidates By Leveraging Our Proprietary Drug Discovery and Optimization Platform and Our Understanding of Nuclear Transport. To date, we have identified Selinexor, other SINE compounds including KPT-350, a series of PAK4 inhibitors and Verdinexor through our drug discovery and optimization platform. We plan to continue to leverage our understanding of nuclear transport and our platform in our efforts to discover additional drug candidates in the form of specific nuclear transport inhibitors that promote the death of diseased cells while sparing normal cells.

Collaborate with Key Opinion Leaders to Conduct Investigator-Sponsored Trials of Selinexor. A significant part of our strategy for efficiently understanding 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 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.

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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 seven 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 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 most of these tumor suppressor proteins, including those generally referred to as p53, p73, FOXO, pRB, BRCA1 and PP2A.

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when DNA in normal cells begins to fail and 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. They exert their effects on cancer cells once DNA damage is detected by promoting 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.

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-κ B 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 and 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 Selective Inhibitors of Nuclear Export, or SINE

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. 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 **S**elective **I**nhibitors of **N**uclear **E**xport, or **SINE**, compounds. We have discovered SINE compounds by applying our proprietary drug discovery and optimization platform to the recently 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 of 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 the increase of tumor suppressor proteins 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

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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.

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 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 autoimmune and inflammatory diseases, wound healing, HIV and influenza. 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 erythematosis, 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 580,000 people in the United States and 7.6 million people in the world projected to die of cancer in 2014 according to the American Cancer Society. The American Cancer Society also projects that approximately 1.7 million new cancer cases will be diagnosed in the United States in 2014. The International Agency for Research on Cancer projects that, by 2030, 20 million to 26 million people will be diagnosed with cancer, and 13 million to 17 million will die of cancer, each year worldwide.

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 there is evidence to suggest 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

Our Lead Drug Candidate Selinexor (KPT-330)

Overview

Our lead drug candidate, Selinexor (KPT-330), is a wholly-owned, orally available, small molecule, potent SINE compound that specifically blocks XPO1 cargo binding. Selinexor inhibits the export of tumor suppressor proteins out of the nucleus. As a result, these proteins are retained in the nucleus where they can detect cancerous changes and promote the death of cancer cells. We are currently conducting three open-label Phase 1 clinical trials of Selinexor, the first in patients with heavily pretreated relapsed and/or refractory hematological malignancies, the second in patients with heavily pretreated relapsed and/or refractory solid tumor malignancies, and the third, a food effect study, in patients with metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. We have observed preliminary 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. We believe that the oral

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administration of Selinexor and lack of cumulative or major organ toxicities observed to date in patients treated with Selinexor in our ongoing Phase 1 clinical trials create the potential for its broad use across many cancer types. Assuming continued positive results from our ongoing Phase 1 and Phase 2 clinical trials of Selinexor and pending regulatory feedback, we plan to initiate registration-directed clinical trials of Selinexor in three hematological malignancy indications during 2014. We expect to initiate these clinical trials for Selinexor in AML, DLBCL and Richter's Syndrome. We plan to seek regulatory approvals of Selinexor in North America and Europe in each such indication 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 Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014. We intend to enter into collaborations for marketing and commercialization of Selinexor in particular geographies at an appropriate time.

In May 2012, we filed two investigational new drug applications, or INDs, with the U.S. Food and Drug Administration, one covering Selinexor in advanced hematological malignancies and the other covering Selinexor in advanced or metastatic solid tumor malignancies. The trials in patients with these two indications were initiated in mid-2012 and are being conducted at cancer centers in the United States, Canada and Denmark. In July 2013, we began enrollment in our third Phase 1 clinical trial of Selinexor, a food effect study that is being conducted in the United States and Canada. We are also gathering additional safety and efficacy data regarding Selinexor as part of the food effect study. To date, over 240 patients have received Selinexor in these three clinical trials.

Advanced Hematological Malignancies

Our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies continues to enroll patients with documented progressive disease at the time of enrollment. These patients have relapsed and/or refractory hematological malignancies, meaning that their cancers are no longer responsive, or were never responsive, to treatment with approved and/or experimental therapies. These patients had received multiple previous treatments, which we refer to as heavily pretreated.

There are six arms to this clinical trial:

Arm 1 includes patients with the following chronic B-cell malignancies: multiple myeloma, or MM, Waldenström's Macroglobulinemia, or WM, chronic lymphocytic leukemia, or CLL, Richter's Syndrome, or RS, and Non-Hodgkin's Lymphoma, or NHL, including NHL that has transformed from slowly growing, or indolent, to aggressive, or Transformed NHL, DLBCL, mantle cell lymphoma, or MCL, and follicular lymphoma, or FL.

Arm 2 includes patients with AML of any subtype except one specified subtype known as M4.

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 with MM or WM taking 20 mg/m^2 of dexamethasone with each dose of Selinexor.

We designed this open-label Phase 1 clinical trial to evaluate the safety of Selinexor, to determine the Phase 2 clinical trial dose and dosing schedule and to evaluate preliminary anti-cancer activity of Selinexor. Currently, Selinexor is orally administered twice per week over a 28-day cycle at up to 80 mg/m^2. We expect to treat up to approximately 250 patients over the course of this clinical trial, with approximately 125 patients expected to be evaluated in Arm 1 and approximately 75 patients expected

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to be evaluated in Arm 2. We expect to treat up to approximately 12, eight, six and 20 patients in Arms 3, 4, 5 and 6, respectively.

Arm 1. As of December 4, 2013, a total of 60 patients on Arm 1 (26 with MM, three with WM, 23 with NHL, four with CLL and four with RS) have been enrolled at doses ranging from 3 mg/m^2 to 45 mg/m^2 at eight clinical centers in the United States, Canada and Denmark. We have observed preliminary evidence of anti-cancer activity in certain of these heavily pretreated patients. Potential responses include CR, which for CLL means complete remission and for the other indications listed means complete response, PR, which for CLL means partial remission and for the other indications listed means partial response, MR, which means minimal response for all indications listed and SD, which means stable disease for all indications listed, each as determined in accordance with commonly accepted evaluation criteria for the specific indication. 45 of the 55 patients (82%) evaluated as of December 4, 2013 in this arm have experienced PR, MR or SD. The distribution of these responses across indications as of December 4, 2013 was as follows: a partial response or partial remission in nine patients, one in each of MM, RS, MCL and FL, two in CLL and three in DLBCL; a minimal response in seven patients, four in MM and three in WM; and stable disease in 29 patients, 15 in MM, five in DLBCL, one in MCL, four in FL, two in CLL and two in RS. Eight of the 55 patients (15%) evaluated as of December 4, 2013 in this arm have experienced PD, including four patients with MM, two patients with DLBCL and two patients with transformed NHL. As of December 4, 2013, five patients either had not yet been evaluated or were deemed 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 therapeutic protocol for the trial.

Responses are shown in the table below for the 55 patients who had been evaluated as of December 4, 2013, each of whom received a dose between 3 mg/m^2 to 45 mg/m^2 per cycle. As of December 4, 2013, patients receiving a dose higher than 45 mg/m^2 had not yet been evaluated. These responses are interim unaudited data based on site reports and are measured using commonly accepted evaluation criteria for the specific indication.

Responses in Arm 1 (Chronic B-Cell Malignancies) [3 mg/m^2 to 45 mg/m^2] as of December 4, 2013

Cancer	Number of Patients Evaluated	Total PRs, MRs and SD (%)	PR (%)	MR (%)	SD (%)	PD	WC
MM	25	20 (80%)	1 (4%)	4 (16%)	15 (60%)	4 (16%)	1 (4%)
WM	3	3 (100%)		3 (100%)			
CLL	4	4 (100%)	2* (50%)		2 (50%)		
RS	3#	3 (100%)	1 (33%)		2 (67%)		
NHL							
DLBCL	10	8 (80%)	3 (30%)		5 (50%)	2 (20%)	
MCL	2	2 (100%)	1 (50%)		1 (50%)		
FL	6	5 (83%)	1 (17%)		4 (67%)		1 (17%)
Transformed	2					2 (100%)	
Total	**55 (100%)**	**45 (82%)**	9 (16%)	7 (13%)	29 (53%)	**8 (15%)**	**2 (4%)**

* These PRs in CLL patients refer to lymph node response only.

\# We previously reported that four patients with Richter's Syndrome were evaluated as of December 4, 2013. One of these four patients was subsequently deemed non-evaluable as of December 4, 2013 and is not included in the response data presented here.

PD means progressive disease, as determined in accordance with commonly accepted evaluation

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criteria for the specific indication. Withdrew consent, or WC, means a patient withdrew from the trial before evaluation. Patients who have not yet been evaluated or are considered non-evaluable are not included in the response data.

Enrollment in this arm began in July 2012. In order to remain on study, patients must exhibit a response of SD or better at each evaluation, which typically occurs at the end of each 28-day dosing cycle. A response of SD represents a stabilization of the disease, as determined in accordance with commonly accepted evaluation criteria for the specific indication, over one dosing cycle, which we believe is an indicator of the anti-cancer effect of the drug candidate. As of December 4, 2013, fifteen patients in this arm remained on study. As of December 4, 2013, five patients had remained on study in this arm for longer than nine months, including two patients who had been on study for longer than twelve months and one patient who had been on study for longer than 15 months. Three of the five patients continued to remain on study as of December 4, 2013. No major organ toxicities have been observed in this arm to date.

The most common side effects in this arm, known as adverse events, or AEs, are Grade 1 or Grade 2 adverse events. Grade 1 and 2 adverse events are generally characterized as mild. Grade 3 adverse events are considered moderate and Grade 4 adverse events are considered severe. As of December 4, 2013, we have reports of AEs in 55 of the 60 patients enrolled in this arm and the AE prevalence percentages below are based upon the 59 patients from whom we have collected safety data as of December 4, 2013. Gastrointestinal adverse events and fatigue are the most common types of adverse events seen in Arm 1. As of December 4, 2013, the gastrointestinal events typically consist of nausea in 41 patients (69%), anorexia in 31 patients (53%), vomiting in 20 patients (34%) and diarrhea in 18 patients (31%). The gastrointestinal events are solely either Grade 1 or Grade 2 events and are generally responsive to standard supportive care. Grade 1 or Grade 2 fatigue was observed in 30 patients (51%) in this arm as of December 4, 2013, with three additional patients (5%) showing Grade 3 fatigue. We have also observed Grade 3 or Grade 4 thrombocytopenia, or low count of platelets in the blood, in 14 patients (24%), with four additional patients (7%) showing Grade 1 or Grade 2 thrombocytopenia. We have also observed Grade 3 or Grade 4 neutropenia, or low neutrophil counts, in 13 patients (22%), with four additional patients (7%) showing Grade 1 or Grade 2 neutropenia. We expect that thrombocytopenia and neutropenia are primarily a result of patients entering this arm with marked bone marrow suppression due to both disease and prior therapies. We do not gather data regarding the number of patients that have withdrawn from this arm as a result of AEs.

Due to the gastrointestinal events we observed earlier in the arm, we now instruct physicians to initiate supportive care and medications prior to patients beginning on Selinexor therapy. The supportive care consists primarily of focusing on maintaining caloric and fluid intake as well as the introduction of appetite stimulants and anti-nausea medication. We have seen fewer and milder gastrointestinal events and reduced fatigue as a result of the initiation of supportive care and medications prior to beginning Selinexor therapy.

As of December 4, 2013, there have been 51 serious adverse events, or SAEs, reported in 23 patients in Arm 1. 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. SAEs may be attributed to Selinexor or deemed unrelated. Of the 51 SAEs reported as of December 4, 2013, one SAE was deemed by us and the clinical investigator to be related to Selinexor. This SAE was Grade 2 blurred vision. This was not permanent and the patient recovered from this SAE. All patients in this arm at the time received eye examinations by an ophthalmologist and all new patients receive the same examination prior to beginning treatment in order to assess any changes in vision while on Selinexor therapy.

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No dose limiting toxicities, or DLTs, were observed at the 30 mg/m^2 or above dose levels in Arm 1. We are continuing with dose escalation and fixed dose expansion cohorts in Arm 1.

Arm 2. As of December 4, 2013, a total of 39 patients with heavily pretreated relapsed and/or refractory AML were enrolled in this arm and the majority of these patients are elderly, meaning 60 years of age or older. We have observed preliminary evidence of anti-cancer activity in certain of the patients in this arm. Potential responses include CR, which for AML means complete remission with complete blood count recovery, CR(i), which for AML means complete remission with incomplete blood count recovery, PR, which for AML means partial remission, MLFS, or morphologic leukemia-free state and SD. Seventeen of the 33 patients (52%) evaluated as of December 4, 2013 in this arm have experienced a CR, CR(i), PR, MLFS or SD. Five patients experienced CR or CR(i), with four patients experiencing CR and one patient experiencing CR(i), two patients have experienced PR, one patient has experienced MLFS and nine patients have experienced SD. Twelve of the 33 patients (36%) evaluated as of December 4, 2013 in this arm have experienced PD. Six patients had not yet been evaluated or were non-evaluable as of December 4, 2013.

Responses are shown in the table below for the 33 patients who had been evaluated as of December 4, 2013, each of whom received a dose between 16.8 mg/m^2 to 55 mg/m^2 per cycle. These responses are interim unaudited data based on site reports and are measured using commonly accepted evaluation criteria for AML.

Responses in Arm 2 (AML) [16.8 mg/m^2 to 55 mg/m^2] as of December 4, 2013

Number of Patients Evaluated	Total CRs, CR(i)s, PRs, MLFS and SD (%)	CR (%)	CR(i) (%)	PR (%)	MLFS (%)	SD (%)	PD (%)	WC (%)
33	17 (52%)	4 (12%)	1 (3%)	2 (6%)	1 (3%)	9 (27%)	12 (36%)	4 (12%)

Enrollment in this arm began in January 2013. In order to remain on study, patients must exhibit a response of SD or better at each evaluation, which typically occurs at the end of each 28-day dosing cycle. A response of SD represents a stabilization of the disease, as determined in accordance with commonly accepted evaluation criteria for AML, over one dosing cycle, which we believe is an indicator of the anti-cancer effect of the drug candidate. As of December 4, 2013, five patients in this arm remained on study. As of December 4, 2013, five patients had remained on study in this arm for more than three months. Two of these patients continued to remain on study as of December 4, 2013. No major organ toxicities have been observed in this arm to date.

Gastrointestinal adverse events and fatigue are the most common types of AEs seen in Arm 2. As of December 4, 2013, we have reports of AEs in 36 of the 39 patients enrolled in this arm and the AE prevalence percentages below are based upon 38 patients from whom we have collected safety data as of December 4, 2013. As of December 4, 2013, the gastrointestinal adverse events typically consist of nausea in 22 patients (58%), anorexia in 17 patients (45%), vomiting in 13 patients (34%), diarrhea in 12 patients (32%) and weight loss in 10 patients (26%). The gastrointestinal events are primarily Grade 1 or Grade 2 events (95%) that are generally responsive to standard supportive care. Fatigue was observed in 18 patients in this arm (47%) as of December 4, 2013, including Grade 3 fatigue in 3 patients (8%) and Grade 1 or Grade 2 fatigue in 15 patients (40%). We have also observed Grade 4 thrombocytopenia in 3 patients (8%) in this arm as of December 4, 2013. We expect that the thrombocytopenia is primarily a result of patients entering this arm with marked bone marrow suppression due to both disease and prior therapies. We do not gather data regarding the number of patients that have withdrawn from this arm as a result of AEs.

As in Arm 1, we have seen fewer and milder gastrointestinal events and reduced fatigue as a result of the initiation of supportive care and medications prior to beginning Selinexor therapy.

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As of December 4, 2013, there have been 54 SAEs reported in 25 patients in Arm 2. Of the 54 SAEs reported, one SAE was deemed by us and the clinical investigator to be related to Selinexor. This SAE was the worsening of a patient's existing cataracts. We do not have data with respect to the status of this SAE.

As of December 4, 2013, no DLTs have been observed in this arm.

Arm 3. We are evaluating Selinexor in patients with heavily pretreated relapsed and/or refractory T-cell lymphoma in Arm 3 of this clinical trial. We began enrollment in August 2013 and have administered Selinexor to one patient in Arm 3 who was non-evaluable as of December 4, 2013.

Arms 4 6. As of December 4, 2013, we have not evaluated any patients in these arms of our Phase 1 clinical trial in hematological malignancies. We expect to treat approximately eight patients in Arm 4, six patients in Arm 5 and 20 patients in Arm 6.

Advanced or Metastatic Solid Tumor Malignancies

Our Phase 1 clinical trial of Selinexor in patients with advanced or metastatic solid tumor malignancies continues to enroll patients with documented progressive disease at the time of enrollment. These patients have heavily pretreated relapsed and/or refractory solid tumor malignancies. We have treated patients diagnosed with colorectal cancer, or CRC, squamous cell cancer of the head and neck or lung, ovarian cancer, cervical cancer, endometrial stromal sarcoma, or ESS, melanoma, glioblastoma, or GBM, pancreatic cancer, prostate cancer and other solid tumor malignancies. We designed this open-label Phase 1 clinical trial to evaluate the safety of Selinexor, to determine the Phase 2 clinical trial dose and dosing schedule and to evaluate preliminary anti-cancer activity of Selinexor. Selinexor is orally administered in escalating dose levels two times per week over each 28-day cycle. We expect to treat up to approximately 90 patients over the course of the initial dose escalation phase of this clinical trial. We expect to evaluate approximately 74 additional patients in fixed dose expansion cohorts of this trial at the expected Phase 2 clinical trial dose.

As of December 24, 2013, a total of 112 patients have been enrolled at six clinical centers in the United States, Canada and Denmark, and are being treated at doses ranging from 3 mg/m^2 to 65 mg/m^2. We have observed preliminary evidence of anti-cancer activity in certain of the patients in this trial. Potential responses include CR, PR and SD, each as determined in accordance with Response Evaluation Criteria In Solid Tumors, or RECIST, the commonly accepted evaluation criteria for solid tumor malignancies. Forty-five of the 94 patients (48%) evaluated as of December 24, 2013 in this trial have experienced a PR or SD, including a PR in three patients; 42 patients have experienced SD. Forty-nine of the 94 patients (52%) evaluated as of December 24, 2013 in this trial have experienced PD. Eighteen patients had not yet been evaluated or were non-evaluable as of December 24, 2013.

Responses are shown in the table below for the 94 patients who had been evaluated as of December 24, 2013, each of whom received a dose between 3 mg/m^2 to 65 mg/m^2 per cycle. These responses are interim unaudited data based on site reports and are evaluated in accordance with RECIST.

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Responses in Advanced or Metastatic Solid Tumor Malignancies [3 mg/m^2 to 65 mg/m^2] as of December 24, 2013

Cancer	Number of Patients Evaluated	Total PRs and SD (%)	PR (%)	SD (%)	PD (%)
CRC	35	13 (37%)	1 (3%)	12 (34%)	22 (63%)
Head & Neck	13	9 (69%)		9 (69%)	4 (31%)
Lung	5	3 (60%)		3 (60%)	2 (40%)
Ovarian	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
Cervical	4	2 (50%)		2 (50%)	2 (50%)
Endometrial Stromal Sarcoma	6	5 (83%)		5 (83%)	1 (17%)
Melanoma	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Pancreas	4				4 (100%)
Prostate	5	5 (100%)		5 (100%)	
Other	9	3 (33%)		3 (33%)	6 (67%)
GBM	5				5 (100%)
Total	**94 (100%)**	**45 (48%)**	3 (3%)	42 (45%)	**49 (52%)**

Enrollment in this trial began in June 2012. In order to remain on study, patients must exhibit a response of SD or better at each evaluation, which typically occurs following the completion of two 28-day dosing cycles. A response of SD represents a stabilization of the disease, as determined in accordance with RECIST, over one dosing cycle, which we believe is an indicator of the anti-cancer effect of the drug candidate. As of December 24, 2013, 26 patients in this clinical trial remained on study. As of December 24, 2013, 11 patients had remained on study for more than six months, including two patients on study for longer than eight months, and one patient had remained on study for longer than 17 months. Five of the 11 patients on study for more than six months remained on study as of December 24, 2013. No major organ toxicities have been observed in this trial to date.

The most common AEs associated with Selinexor in patients with advanced or metastatic solid tumor malignancies are gastrointestinal in nature or fatigue. As of December 24, 2013, we have reports of AEs in 106 of the 112 patients enrolled in this arm and the AE prevalence percentages below are based upon 112 patients from whom we have collected safety data as of December 4, 2013. As of December 24, 2013, the gastrointestinal adverse events typically consist of nausea in 74 patients (66%), anorexia in 66 patients (59%), vomiting in 54 patients (48%), dysgeusia, or a distortion in the sense of taste, in 35 patients (31%), weight loss in 37 patients (33%) and diarrhea in 30 patients (27%). The gastrointestinal events are primarily Grade 1 or Grade 2 events (94%) that are generally responsive to standard supportive care. Fatigue was observed in 83 patients (74%) as of December 24, 2013, including Grade 3 fatigue in 16 patients (14%) and Grade 1 or Grade 2 fatigue in 67 patients (60%). Anemia, or a decrease in red blood cell count, was observed in 30 patients (27%) as of December 24, 2013, including Grade 3 anemia in 8 patients (7%) and Grade 1 or Grade 2 anemia in 22 patients (20%). As of December 24, 2013, seven patients have withdrawn from this trial as a result of AEs.

As in our hematological malignancy clinical trial, we have seen see fewer and milder gastrointestinal events and reduced fatigue as a result of the initiation of supportive care and medications prior to beginning Selinexor therapy.

As of December 24, 2013, there have been 89 SAEs reported in 43 patients in this clinical trial. Of the 89 SAEs reported, three were deemed by us and the applicable clinical investigator to be related to Selinexor. One of these SAEs was dehydration and the other two were the development or worsening of cataracts. These SAEs were not permanent and the patients recovered following supportive care.

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As of December 24, 2013, no DLTs were observed in the initial six cohorts at doses ranging from 3 to 30 mg/m^2. Of the three patients who received 10 doses per cycle at 40 mg/m^2, there were two DLTs. One was Grade 3 anorexia with dehydration and fatigue, and the other was Grade 3 fatigue with Grade 1-2 anorexia. Although we believe that neither of these patients with DLTs received optimal supportive care, given the overall clinical picture, we made the decision to establish 10 doses per cycle at 30 mg/m^2 to be the maximum tolerated dose for advanced or metastatic solid tumor malignancy patients. As a result of our decision regarding the maximum tolerated dose, the dose of a third patient being treated at 40 mg/m^2, who had tolerated therapy well, was also reduced to 30 mg/m^2. We have also evaluated 10 additional patients at 10 doses per cycle at 30 mg/m^2 and no DLTs were observed.

We are evaluating a dosing schedule of eight doses per cycle. At eight doses per cycle, a maximum tolerated dose has not yet been established and no DLTs have been observed. Currently, a dose of 85 mg/m^2 at eight doses per cycle is being evaluated in patients with solid tumor malignancies. We are continuing with dose escalation and fixed dose expansion cohorts in this clinical trial.

Metastatic, Locally Advanced or Locally Recurrent Soft Tissue or Bone Sarcomas (Food Effect Study)

In July 2013, we began enrollment in our third clinical trial of Selinexor, a Phase 1b open-label food effect study in heavily pretreated patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. The trial is primarily designed to evaluate the effects of food and formulation (capsules and tablets) on the absorption of oral Selinexor. We are also gathering additional safety and efficacy data regarding Selinexor in this trial. We are currently using the capsule formulation in our other Phase 1 clinical trials. As of December 24, 2013, 19 patients have been enrolled in this clinical trial and sixteen were evaluable for response. We plan to enroll up to approximately 20 patients in this study in the United States and Canada. In light of the results that we have seen in this trial to date, we believe that the new tablet formulations of Selinexor have similar pharmacokinetics and tolerability as the original capsule formulations that are used in our Phase 1 studies. We have also confirmed that Selinexor is better absorbed when taken with food. We expect to use the tablet formulation in our registration-directed clinical trials for Selinexor in hematological indications and our Phase 2 clinical trials for Selinexor in solid tumor malignancies.

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 greater than eight months, and in some cases, over one year. 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 AEs and SAEs 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. Assuming continued positive results from our ongoing Phase 1 and Phase 2 clinical trials of Selinexor and pending regulatory feedback, we plan to initiate registration-directed clinical trials of Selinexor in three hematological malignancy indications during 2014. We expect to initiate these clinical trials for Selinexor in AML, DLBCL and Richter's Syndrome. We plan to seek regulatory approvals of Selinexor in North America and Europe in each such indication 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 Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014.

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Acute Myeloid Leukemia in Elderly Patients

Acute myeloid leukemia, or 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 18,860 new cases of AML, most of which will be in adults, will be diagnosed in the United States in 2014. Given the shift in demographics in the population in the Western hemisphere, it is likely that an increased number of elderly individuals will be diagnosed with this form of cancer. Aside from a general increase in the incidence of AML in the general population, three additional patient populations are contributing to the increasing number of AML cases: an increasing number of older persons are developing a disease called myelodysplastic syndrome, or MDS, which can convert to AML; certain types of chemotherapy, such as alkylating agents used to treat Hodgkin's disease, breast cancer, and other disorders, can increase the risk of developing AML later in life; and patients with chronic myelogenous leukemia treated long term with imatinib (Gleevec) and other drugs can have their disease reach an accelerated or blast phase, converting to AML.

About 40% of AML patients are young enough and fit enough to undergo bone marrow transplantation for their AML, and about 50% of these patients can be cured of their disease. Those that are not cured, and patients who are elderly or unfit for transplant, have a very poor prognosis. The median survival for elderly patients with AML is less than a year and worsens continuously with advancing age to as low as one month for those who are older than 85 years of age. The obstacles to effective therapy in older patients include their heightened susceptibility to drug-related toxicity, which is often due to co-existing medical problems and/or poor organ function, and their lower response to chemotherapy. In addition, the poorer response to therapies in elderly AML patients is due to a higher frequency of high-risk cytogenetic lesions, a type of DNA mutation, compared with their younger counterparts with AML. Even for those elderly patients able to tolerate chemotherapy, complete remission rates are well less than half the complete remission rates for younger adults: about 25 percent in patients older than 70 years old compared to 70 percent in patients younger than 50 years old. In addition, the cases of elderly AML that arise from MDS, or the ineffective production of the myeloid class of blood cells, mean that there are few normal stem cells for those patients available for hematologic recovery after chemotherapy. As a result, complications, hospitalizations and deaths from cytopenias, or reductions in the number of certain blood cells, are common among the elderly with AML.

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. Preclinical data on our SINE compounds from several groups at Dana-Farber Cancer Institute, Ohio State University and MD Anderson Cancer Center have shown preliminary evidence of anti-cancer activity of our SINE compounds against a set of AML cell lines with diverse genetics, as well as against leukemia stem (initiating) cells. In addition, in our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies, as described above, we have observed preliminary evidence of anti-cancer activity of Selinexor in elderly patients (those over 60 years of age) with heavily pretreated relapsed and/or refractory AML. We have observed CRs, CR(i)s, PRs, MLFS or SD in 48% of these patients as of December 4, 2013 and, in many cases, the response has been maintained for longer than two months. We believe that these initial results suggest that Selinexor has the potential to demonstrate anti-cancer activity and tolerability in elderly patients with heavily pretreated AML.

Based on the results observed to date in our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies and the expansion cohort in Arm 2 of this trial consisting primarily of elderly patients with AML, we expect to initiate a randomized, registration-directed Phase 2 clinical trial of Selinexor in patients over 60 years of age with AML in first relapse who are not candidates for intensive chemotherapy or transplantation. The Phase 2 trial is expected to enroll about 150 patients who will be randomized so that for every three patients, two receive Selinexor and

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one receives the treating physician's choice. The physician's choice includes best supportive care, or BSC, which includes transfusions, antibiotics and growth factors as appropriate, or BSC with low dose Ara-C, or BSC with a hypomethylating agent such as azacytidine or decitabine. There are currently no approved agents for these patients, and there are no generally recognized standards of care in this population. The primary endpoint is overall survival. Selinexor will be given at a dose of 55 mg/m^2, administered orally twice per week. The trial is expected to begin in the first half of this year and is expected to take two years to complete.

Diffuse Large B-Cell 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). According to the American Cancer Society, about 70,800 patients will be diagnosed with NHL in the United States in 2014. Diffuse large B-cell lymphoma, or DLBCL, is the most common of the aggressive NHLs, accounting for about one out of every three newly-diagnosed cases of NHL in the United States, according to the American Cancer Society. According to the Leukemia and Lymphoma Society, NHL rates, including DLBCL, have steadily increased 3 to 4% each year in the United States from 1973 to the mid-1990s.

These increases in NHL rates have been observed across all major demographic groups (except for the very young), without a clear cause. Such temporal increases in incidence of a particular form of cancer are atypical. Improved cancer reporting, more sensitive diagnostic techniques, particularly for borderline lesions, changes in classification of lymphoproliferative diseases, which are diseases where lymphocytes are produced in excessive quantities, and, in particular, the increasing occurrence of AIDS-associated DLBCL, have contributed to the escalation of incidence of this disease. Non-AIDS related NHL incidence rates have continued to increase, specifically the rates among females, older males and blacks. For the vast majority of patients, the etiology of DLBCL is unknown.

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®) leads to responses in greater than 75% of patients. In patients who are less than 65 years old, and who have good organ function, high dose chemotherapy with stem cell transplantation can lead to cures in approximately 50% of these patients. 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 and the immunomodulatory drug lenalidomide (Revlimid®) have shown activity in the immunoblastic (activated B cell) type of DLBCL in clinical trials, but responses are generally short-lived. Responses are much lower in the germinal center, or GC, type of DLBCL. Therefore, we believe that novel, well-tolerated drugs are needed for the treatment of relapsed DLBCL, particularly because ibrutinib and Revlimid have not been approved by the FDA for the treatment of DLBCL.

In our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies, Selinexor has shown preliminary evidence of anti-cancer activity in patients with DLBCL. As of December 4, 2013, eight out of 10 patients (80%) evaluated with DLBCL have responded to treatment and the response has been maintained in four of these eight patients (50%) for longer than two months. Based on the results observed to date in this Phase 1 clinical trial, we expect to initiate a randomized, registration-directed clinical trial for Selinexor in DLBCL in late summer 2014. This trial is expected to enroll approximately 300 DLBCL patients who have progressed after at least two lines of chemotherapy and anti-CD20 monoclonal antibodies. This trial will be randomized so that for every three patients, two receive Selinexor and one receives the treating physician's choice of chemotherapy. The primary endpoint is progression free survival. Selinexor will be given at a dose of 60 mg/m^2, administered orally twice per week.

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Richter's Syndrome

Richter's Syndrome (also called Richter's Transformation) describes the transformation from chronic lymphoctic leukemia, or CLL, to DLBCL, a type of NHL. The American Cancer Society estimates that 15,720 patients will be diagnosed with CLL in the United States in 2014. Approximately 5% to 10% of patients with CLL will experience Richter's Syndrome, which is characterized by a distinct worsening of symptoms. Although there are no specific therapies approved to treat Richter's Syndrome, multi-agent chemoimmunotherapy is typically used as a first line treatment.

In our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies, Selinexor has shown preliminary evidence of anti-cancer activity in patients with Richter's Syndrome. As of December 4, 2013, three out of three patients (100%) evaluated with Richter's Syndrome have responded to treatment. Based on the results observed to date in this Phase 1 clinical trial, we are also planning to initiate a registration-directed, single arm clinical trial in the middle of 2014 that is expected to enroll approximately 50 patients with Richter's Syndrome whose disease has relapsed after initial treatment, which is typically multi-agent chemoimmunotherapy. This clinical trial will not be randomized as there are no generally accepted second-line treatments for Richter's Syndrome and, therefore, no available therapies to serve as a control arm for the trial. Consequently, the primary endpoint is overall response rate. Selinexor will be administered orally twice per week at a dose that has not yet been determined.

Multiple Myeloma

Multiple myeloma, or 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 24,050 new cases of MM in 2014. M protein, produced by most MM tumors, has been an established biomarker of the disease and the extent of the disease for over 30 years. More recently, the measurement of a fragment of the M protein, the free light chain, has been used as an additional biomarker of the disease and the extent of the disease in a subset of MM patients.

The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, and the subsequent introduction of the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib. 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. However, despite the increased effectiveness of the first-line agents, the majority of patients will eventually relapse and become drug-resistant. Although a wide variety of new agents are being used in relapsed and/or refractory patients, including new proteasome inhibitors (carfilzomib, ixazomib, oprozomib, and marizomib), immunomodulatory drugs (pomalidomide), monoclonal antibodies (elotuzumab and daratumumab), a signal transduction modulator (perifosine), and histone deacetylase inhibitors (vorinostat and panobinostat), we believe that there remains a need for therapies in these relapsed and/or refractory patients that can improve the overall survival rate.

In our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies, Selinexor has shown preliminary evidence of anti-cancer activity in patients with MM. As of December 4, 2013, 25 MM patients had been evaluated in our trial. Twenty of the 25 patients (80%) with progressive MM on entry experienced either a PR, an MR or SD, while four of 25 (16%) had PD. The remaining patient withdrew from the trial. Some of these patients experiencing either a PR, an MR or SD have a form of MM called light chain disease. Patients with light chain MM generally have a prognosis that is worse than patients with usual MM, where the myeloma protein is composed of

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both light and heavy chains. Light chain MM represents approximately 15% to 20% of MM cases and generally does not respond to therapies as well as the usual MM. Given the preliminary responses of patients with light chain MM observed to date in our Phase 1 clinical trial of Selinexor in patients with advanced hematological malignancies, and the unmet medical need in light chain MM, we may decide to initiate additional clinical trials of Selinexor in light chain MM. If we are able to confirm the preliminary evidence of anti-cancer activity of Selinexor in our expansion cohort of MM patients, including both usual and light chain MM, we may decide to initiate a registration-directed clinical trial in MM.

Solid Tumors and Other Cancer Indications

We have also observed preliminary evidence of anti-cancer activity of Selinexor in our Phase 1 clinical trial of patients with advanced or metastatic solid tumor malignancies. We have initiated Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014.

We also expect a number of investigator sponsored trials, or ISTs, to be initiated in a variety of both hematological and solid tumor malignancies in 2014. These ISTs could consist of single agent or combination studies with other agents in both hematological and solid tumor malignancies.

Preclinical Studies

Selinexor was administered in efficacy studies to mice implanted with human tumors, or xenografts. We observed evidence of anti-cancer activity of Selinexor in mouse models of myeloma, MCL and T-cell acute lymphocytic leukemia xenografts. In addition, we observed anti-cancer activity of Selinexor, including survival advantages in models of orthotopic MM, and in several NHL xenografts, as well as in orthotopic leukemia models of AML, ALL and CLL. We have also observed evidence of anti-cancer activity of Selinexor in solid tumor xenografts including prostate, breast, neuroblastoma, melanoma, lung, glioblastoma, alveolar soft part sarcoma, colon and ovarian cancers. In addition, we performed preclinical studies of Selinexor in combination with paclitaxel, velboraf (B-raf inhibitor), irinotecan, topotecan and radiation therapy. In all of these preclinical studies of Selinexor in combination with other drugs, we observed evidence of additive and/or synergistic effects with inhibition of tumor growth. In addition, we have observed evidence of anti-cancer activity with Verdinexor, an oral SINE compound closely-related to Selinexor, in dogs with newly-diagnosed or first relapse after chemotherapy lymphomas.

Our Other Drug Candidates

KPT-350 and Related SINE Compounds

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 κB, or NF-κB, is a protein that plays very important roles in many types of inflammation. In cells, NF-κB can be inhibited by another protein called IκB, or Inhibitor of NF-κB, that binds to NF-κB and prevents NF-κB from binding to DNA and driving inflammation. When inflammation occurs, XPO1 transports IκB out of the nucleus into the cytoplasm where it cannot inhibit NF-κB activity. When KPT-350 or a similar SINE compound inhibits XPO1, IκB export to the cytoplasm is blocked and IκB accumulates in the nucleus. The IκB in the nucleus binds to NF-κB and blocks its inflammatory activity. KPT-350 or a similar SINE compound also increases the concentration of other inhibitors of NF-κB in the nucleus such as FOXO and COMMD1 proteins. Thus, XPO1 inhibition leads to potent, multifaceted inhibition of the inflammatory mediator NF-κB.

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KPT-350 and similar SINE compounds have additional important anti- inflammatory activities such as activation of the proteins RXRγ, PPARγ and NRF2 (an anti-oxidant and neuroprotective protein). Finally, 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 SINE compounds have shown broad evidence of anti-inflammatory activity across preclinical models of the following diverse autoimmune diseases: 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

In addition to our SINE compounds, we also investigate XPO1 cargo proteins and their role in cell cycle and 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 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 change. Based on this biology, we used our drug discovery and optimization platform to identify small molecule inhibitors of PAK4. Our PAK4 inhibitors have shown broad evidence of anti-cancer activity against hematological and solid tumor malignancies cells while showing minimal toxicity to normal cells *in vitro*. In mouse xenograft studies, our PAK4 inhibitors given orally have shown evidence of anti-cancer activity and tolerability. If we confirm these preliminary results in future preclinical studies, we may initiate IND-enabling toxicology studies with one or more PAK4 inhibitors.

Verdinexor (KPT-335)

We have used spontaneously occurring dog cancers as a surrogate model for human malignancies. It is widely known that canine lymphomas respond to chemotherapy similarly to their human counterpart (human NHL) and display a comparable genetic profile. 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 Minor Use / Minor Species, or MUMS, designation from the Center for Veterinary Medicine, or CVM, of the FDA for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in dogs with Verdinexor.

Several different dog tumor cell lines including those derived from lymphomas exhibited growth inhibition and apoptosis *in vitro* upon exposure to nanomolar concentrations of Verdinexor. A Phase 1 clinical trial of Verdinexor was performed in dogs with cancer, primarily with lymphoma. The maximum tolerated dose was 35 mg/m^2 twice per week although biological activity was observed at 20 mg/m^2. PR or SD, in each case for at least 4 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 30 mg/m^2 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

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with either newly-diagnosed or first relapse after chemotherapy lymphomas. Verdinexor was administered initially at doses ranging from 25 mg/m^2 to 30 mg/m^2 two or three days per week. Minimal or no supportive care was given. The total CRs and PRs of the 58 dogs was 34%, with one CR and 19 PRs. An additional 33 of 58 dogs (57%) experienced SD for at least four weeks. The median time to disease progression was approximately five weeks, with 20 dogs (34%) remaining on study for longer than eight weeks. A few dogs 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.

Our Drug Discovery and Optimization Platform

The development of Selinexor, and other drug candidates, including our other SINE compounds and PAK4 inhibitors, as well as Verdinexor, began with our proprietary drug discovery and optimization platform. We intend to continue using this platform, which includes expertise in computational chemistry, our proprietary virtual chemical library and *in silico* screening know- how, certain biochemical assays, and *in silico* complexes of the structures of the target proteins bound with our small molecules, and other trade secrets and know-how.

While our platform can be used to target many protein families, we are focused on the discovery and development of novel inhibitors of nuclear export, particularly those targeting XPO1 and XPO1 cargos. We identified our small molecule inhibitors by using structural insights from X-ray crystallography and molecular modeling approaches, coupled with virtual screening. Initially promising compounds were then evaluated with our proprietary platform to optimize them into drug candidates.

Our ideal drug candidates selectively bind to the target protein and do so in part by forming a covalent bond with a particular cysteine residue in the protein. Cysteine is one of the 20 amino acids that make up proteins and has been useful for forming covalent bonds with drug compounds. Like non-covalent drugs, our compounds selectively bind, or "fit" into a specific binding pocket in the target protein, and don't "fit" well into binding pockets of other proteins. Additionally, our drug candidates form a covalent bond, which introduces a second level of selectivity, meaning that our compounds are less likely to bind inappropriately compared with typical non-covalent drugs. In addition, because covalent drugs can be given infrequently (e.g., once a day or even less), there are potentially fewer off-target effects as there is less need to maintain high drug levels. For example, Selinexor is now administered twice weekly.

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.

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We file patent applications directed to the composition of matter and methods of use and manufacture for our drug candidates. As of March 19, 2014, 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 20 pending patent applications in the United States, four pending international applications filed under the Patent Cooperation Treaty (PCT), one of which is co-owned with a third party, and 59 pending patent applications in foreign jurisdictions. The PCT is an international patent law treaty that provides a unified procedure for filing a single initial patent application to seek patent protection for an invention simultaneously in each of the member states. Although a PCT application is not itself examined and cannot issue as a patent, it allows the applicant to seek protection in any of the member states through national-phase applications. The technology underlying such pending patent applications has been developed by us and was not acquired from any in-licensing agreement.

The intellectual property portfolios for our key drug candidates as of March 19, 2014 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 26 pending foreign patent applications and two pending non-provisional applications in the United States. Any patents that may issue in the United States as part of our Selinexor patent portfolio 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.

Selinexor (Wound Healing): Our patent portfolio covering Selinexor for wound healing covers methods of using Selinexor or Verdinexor for wound healing, and consists of one pending PCT patent 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 one pending non-provisional U.S. patent application and one PCT application that provides the opportunity for seeking protection in all PCT member states. 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 patent portfolio covers both the composition of matter and methods of use of the PAK4 inhibitors described therein and consists of three patent families with nine pending U.S. provisional patent applications and one PCT application in total. The PCT Application provides the opportunity for seeking protection in all PCT member states in one family. Any patents that may issue in the United States based on this PCT application 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. We expect to file non-provisional patent applications claiming the benefit of the provisional applications in the second and third families in the second half of 2014. Any patents that may issue from such applications will expire no earlier than 2034.

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Verdinexor (KPT-335): Our Selinexor patent portfolio described above 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 March 19, 2014, 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.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See " Government Regulation Patent Term Restoration and Extension" below for additional information on such extensions. In the future, if and when our drug candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug candidate and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our drug candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Our issued 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

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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 a large number of companies developing or marketing treatments for cancer and the other indications on which we currently plan to initially focus, including many major pharmaceutical and biotechnology companies. However, to our knowledge, no other company has an XPO1 inhibitor in clinical development at the present time.

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.

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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 for which we currently plan to initially focus, they will compete with the therapies and currently-marketed drugs discussed below.

XPO1 Inhibitors

We have observed preliminary evidence of anti-cancer activity of our XPO1 inhibitor and lead drug candidate, 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. Assuming continued positive results from our ongoing Phase 1 and Phase 2 clinical trials of Selinexor and pending regulatory feedback, we plan to initiate registration-directed clinical trials of Selinexor in three hematological malignancy indications during 2014. We expect to initiate these clinical trials for Selinexor in AML, DLBCL and Richter's Syndrome. We plan to seek regulatory approvals of Selinexor in North America and Europe in each such indication 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 Phase 2 clinical trials of Selinexor in relapsed glioblastoma multiforme and in ovarian, cervical and uterine carcinomas and expect to initiate Phase 2 clinical trials in squamous head, neck or lung cancers and hormone and chemotherapy refractory metastatic prostate cancer during 2014.

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. Elderly patients with AML are often treated with less intensive chemotherapy regimens or drugs called hypomethylating agents because usual chemotherapy has marked toxicities. Once elderly patients with AML experience disease progression while on their initial chemotherapy and/or hypomethylating agent, 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 difficult. An IL3-toxin conjugate (Stemline Inc.) is being evaluated in elderly persons with relapsed and/or refractory AML. A number of other trials with existing anti-cancer drugs (often in combinations) are ongoing in this population.

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan®). 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 and the immunomodulatory drug lenalidomide (Revlimid®) have shown activity in immunoblastic (activated B cell) 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 several different types of chemotherapy. Certain monoclonal antibodies similar to rituximab are also being evaluated in relapsed DLBCL.

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

Currently, there are three commonly-used targeted or novel agents approved in the U.S. for the treatment of patients with MM: Velcade®, Revlimid® and Thalomid®. Other approved agents include Kyprolis®, approved by the FDA on July 20, 2012, and Pomalyst®, approved by the FDA on February 8, 2013, each for the relapsed and/or refractory patient population. Other potentially competitive therapies are in clinical development for MM. Vorinistat, being developed by Merck & Co., and

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panobinostat, being developed by Novartis AG, are being studied in combination with bortezomib for relapsed myeloma, and elotuzumab is being developed by Abbott Laboratories.

Drug compounds currently in preclinical studies, if developed and approved, could also be competitive with our drug candidates, if approved. Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb Company) has evaluated compounds derived from leptomycin B in preclinical studies. CanBas Co., Ltd. has been developing a product referred to as CBS9106, a preclinical XPO1 inhibitor.

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.

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 that compound had poor oral bioavailability 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 supplies from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place. 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 prior to seeking regulatory approval.

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, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, 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.

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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 process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. 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 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 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:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with FDA's good laboratory practice, or GLP, regulations;
- submission to 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;
- 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 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;
- 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 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 studies, 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.

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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, 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 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.

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. 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

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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 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 $554,600 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th 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. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA also may require submission of a REMS plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

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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 Designation

The FDA is authorized to expedite the review of applications for new drug products that are intended, either alone or in combination with other products, for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the disease or condition. Under the fast track program, the sponsor of a drug candidate may request FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for fast track designation within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with FDA, FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides, and FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, 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 FDA if FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Breakthrough Therapies

In 2012, Congress enacted the Food and Drug Administration Safety and Improvement Act or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." Breakthrough therapies are defined as those intended, either alone or in combination with other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Under FDASIA, FDA may take certain actions with respect to products designated as breakthrough therapies, including holding meetings with the sponsor and the review team throughout the development process; providing timely advice to and communication with 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 certain steps to design the clinical trials in an efficient manner.

Accelerated Approval

FDASIA also codified and expanded on FDA's accelerated approval regulations, under which FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit. Under FDASIA, FDA may also grant accelerated approval using a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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.

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A surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. FDASIA lists the types of evidence that may be used to support a finding that an endpoint is reasonably likely to predict clinical benefit. A drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow 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.

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,

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manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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

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

The FDA strictly regulates 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 Act, 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 that the generic product is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "AB" therapeutic equivalence rating to

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mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, FDA's designation of an "AB" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

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 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 indicate 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.

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.

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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.

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 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, the product 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.

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Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of a NDA, plus the time between the submission date of a 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 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 favourable 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 drug 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 drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing

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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.

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 drug if such company can complete a full MAA with a complete database of pharmaceutical test, pre-clinical tests and clinical trials and obtain marketing approval of its product.

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.

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

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at FDA is responsible for determining whether a new veterinary product should be approved on the basis of a NADA filed by the applicant. A NADA must contain substantial evidence of the safety and effectiveness of the animal drug, as well as data and controls demonstrating that the product will be manufactured and studied in compliance with, among other things, applicable cGMP and GLP practices.

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

Safety:	The design and review of the safety study and the study protocol are completed prior to initiation of the study to help assure that the data generated will meet FDA requirements. These studies are conducted under rigorous quality control, including GLP, to assure integrity of the data. They are designed to clearly define a safety margin, identify any potential safety concerns, and establish a safe dose for the product. This dose and effectiveness is then evaluated in the pivotal field efficacy study where the product is studied in the animal patient population in which the product is intended to be used.
Efficacy:	Early pilot studies may be done in laboratory cats or dogs to establish effectiveness and the dose range for each product. When an effective dose is established, a study protocol to test the product in real world conditions is developed prior to beginning the study. The pivotal field efficacy study protocol is submitted for review and concurrence prior to study initiation, to help assure that the data generated will meet requirements. This study must be conducted with the formulation of the product that is intended to be commercialized, and is a multi-site, randomized, controlled study, generally with a placebo control.
CMC:	To assure that the new animal drug product can be manufactured consistently, FDA will require applicants to provide documentation of the process by which the active ingredient is made and the controls applicable to that process that assure the active ingredient and the formulation of the final commercial product meet certain criteria, including purity and stability. After a product is approved, applicants will be required to communicate with FDA before any changes are made to these procedures or at the manufacturing site. Both the active ingredient and commercial formulations are required to be manufactured at facilities that practice cGMP.

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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, 2014, we had 31 full-time employees, 25 of whom were primarily engaged in research and development activities and 13 of whom had an M.D. or Ph.D. degree.

Executive Officers of the Company

The following table lists the positions, names and ages of our executive officers as of March 1, 2014:

Name	Age	Position
Michael G. Kauffman, M.D., Ph.D.	50	Chief Executive Officer and Director
Sharon Shacham, Ph.D., M.B.A.	43	President and Chief Scientific Officer
Paul Brannelly	41	Senior Vice President, Finance and Administration, Secretary and Treasurer

Michael G. Kauffman, M.D., Ph.D. Dr. Kauffman has served as Karyopharm's Chief Executive Officer since January 2011 and has been one of our directors since 2008. Dr. Kauffman co-founded Karyopharm with Dr. Sharon Shacham in 2008 and served as our President from January 2011 to December 2013 and as Chief Medical Officer from December 2012 to December 2013. Prior to joining Karyopharm, he was Chief Medical Officer of Onyx Pharmaceuticals Inc., a biopharmaceutical company, from November 2009 to December 2010, which acquired Proteolix Inc. in November 2009 where he was Chief Medical Officer since November 2008, where he led the development of Kyprolis® (carfilzomib), a novel proteasome inhibitor approved in refractory myeloma by the FDA in July 2012. Prior to joining Onyx Pharmaceuticals, Dr. Kauffman was an operating partner at Bessemer Venture Partners from 2006 to 2008 where he led investments in biotechnology companies. Prior to that, 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, from 2006 to 2008, and 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, where 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

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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, on the board of directors and the audit committee and compensation committee of Zalicus Inc. (formerly CombinatoRx 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 received his B.A. in Biochemistry from Amherst College, his M.D. and Ph.D. from Johns Hopkins Medical School, and trained in internal medicine and rheumatology at Beth Israel (now Beth Israel Deaconness Medical Center) and Massachusetts General Hospitals. He is board certified in internal medicine. We believe Dr. Kauffman's qualifications to serve on our board of directors include his extensive experience in the healthcare industry as well his extensive knowledge of our company and its business since inception through service in multiple executive leadership positions and as a member of our board.

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 platform, which was used for the discovery of Selinexor, our lead drug candidate. Dr. Shacham co-chairs our Scientific Advisory Board. Prior to founding Karyopharm, from July 2000 to April 2009, she was Senior Vice President of Drug Development at Epix Pharmaceuticals, Inc., which underwent liquidation proceedings through an assignment for the benefit of creditors under Massachusetts law in 2009, and Director, Algorithm and Software Development at Predix Pharmaceuticals Inc. which merged 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.

Paul Brannelly. Mr. Brannelly joined Karyopharm in June 2013 as Senior Vice President, Finance and Administration and has served as our Secretary and Treasurer since July 2013. Prior to joining Karyopharm, Mr. Brannelly served most recently as Vice President of Finance at Verastem, Inc., a biopharmaceutical company, from September 2011 to June 2013, Chief Financial Officer from November 2010 to September 2011, and as Treasurer and Secretary from November 2010 to June 2013, where he led the company through the initial public offering process and managed several successful financings. From January 2010 to September 2011, Mr. Brannelly held the position of Chief Financial Officer at the Longwood Fund, a venture capital firm aimed at investing in, managing and building healthcare companies, where he set up the financial and operational infrastructure following the closing of its first fund. From November 2005 to September 2009, he served as Vice President, Finance at Sirtris Pharmaceuticals, Inc., a biopharmaceutical company which GlaxoSmithKline plc purchased for $720 million in 2008, where he managed the S-1 preparation and due diligence process for Sirtris' initial public offering and managed the company's transition to being a public company. Mr. Brannelly started his biopharmaceutical career at Dyax Corporation from September 1999 to May 2002, and subsequently moved on to positions of increasing responsibility at Zalicus Inc. (formerly CombinatoRx Inc.) from May 2002 to November 2005, most recently as VP Finance and Treasurer, where he led Zalicus through the initial public offering process. Mr. Brannelly holds a Bachelors of Business Administration in Accounting from the University of Massachusetts at Amherst.

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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 2 Mercer Road, Natick, Massachusetts 01760. Our telephone number is (508) 975-4820, and our website is located at www.karyopharm.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Form 10-K.

Available Information

Our Internet website is http://www.karyopharm.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended. 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., 2 Mercer Road, Natick, Massachusetts 01760, 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

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shown promising results in early-stage clinical trials may still suffer significant setbacks in subsequent registration clinical trials. Additionally, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later-stage clinical trials and interim results of a clinical trial are not necessarily indicative of final results.

In addition, the design of a clinical trial can determine whether its results will support approval of a drug and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We 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 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 no discussions with the FDA or non-U.S. regulatory authorities regarding the design of our planned registration-directed clinical trials for Selinexor. We plan to commence three such clinical trials of Selinexor during 2014, one in the first half of 2014, another in late summer 2014 and a third during the middle of 2014 and 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. 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 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 an additional Phase 3 clinical trial following completion of our 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.

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The results to date in preclinical studies conducted by us or our academic collaborators and in Phase 1 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. The primary endpoint of the first of our two planned randomized registration-directed clinical trials of Selinexor, planned in patients over 60 years of age with AML in first relapse, who are not candidates for intensive chemotherapy or transplantation, is overall survival. The primary endpoint of the second of our two planned randomized registration-directed clinical trials of Selinexor, planned in patients with DLBCL who have progressed after at least two lines of chemotherapy and anti-CD20 monoclonal antibodies, is progression free survival. We have no clinical data in humans relating to the impact of Selinexor on overall survival; we are gathering information on progression free survival. We have no comparative clinical data between Selinexor and standard or supportive care. If Selinexor does not demonstrate a progression free or 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, following discussions with regulatory authorities, we may use overall response rate as a primary endpoint, as we expect to do in our registration-directed clinical trial of Selinexor in patients with Richter's Syndrome. This trial is expected to evaluate patients whose disease has relapsed after initial treatment, which is typically multi-agent chemoimmunotherapy. This clinical trial will not be randomized as there are no generally accepted second-line treatments for Richter's Syndrome and, therefore, no available therapies to serve as a control arm for the trial. Consequently, the primary endpoint of the trial is expected to be overall response rate. If Selinexor does not demonstrate a sufficient overall response rate for Richter's Syndrome, or any other indication for which a clinical trial has overall response rate as a primary 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;
- 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;

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effectively competing with other therapies;

obtaining and maintaining coverage and adequate reimbursement by third-party payors, including government payors, for any approved drugs;

maintaining a continued 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.

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 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 discovering and developing drug candidates, including through the use of our technology platform, 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.

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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 clinical trials of Selinexor to date are based on unaudited data provided by our clinical trial investigators. An audit of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we currently anticipate. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have 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:

- regulators 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 regulators may require us, to conduct additional 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.

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

- be delayed in obtaining marketing approval for our drug candidates;
- not obtain marketing approval at all;
- obtain marketing approval in some countries and not in others;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements; or
- have the drug removed from the market after obtaining marketing approval.

Our drug development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our drug candidates 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;
- 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.

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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, even though Selinexor has generally been well-tolerated by patients in our Phase 1 clinical trials to date, in some cases there were adverse events, some of which were serious. The most common drug-related adverse events, or AEs, were gastrointestinal, such as nausea, anorexia, diarrhea and vomiting, and fatigue. These side effects were generally mild or moderate in severity. The most common AEs that were Grade 3 or Grade 4, meaning they were more than mild or moderate in severity, were thrombocytopenia, or low count of platelets in the blood, and neutropenia, or low neutrophil counts. A small percentage of patients have withdrawn from our Phase 1 solid tumor malignancy trial as a result of AEs. We do not gather data relating to patient withdrawals as a result of AEs for our other Phase 1 clinical trials. A small percentage of patients across our Phase 1 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.

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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 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

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they are approved, or enter into collaborations with respect to the sale and marketing of our drug candidates.

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.

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

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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 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.

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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;

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 for up to $5.0 million, 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.

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Verdinexor (KPT-335) is our clinical drug candidate for the treatment of pet dogs with newly-diagnosed and first time relapse lymphomas. We submitted the safety and effectiveness sections of a New Animal Drug Application, or NADA, for Verdinexor to the FDA in December 2013. 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 is intended to support regulatory approval under the MUMS designation. We submitted the safety and effectiveness sections of a NADA for Verdinexor to the FDA in December 2013. If this clinical trial of Verdinexor fails to demonstrate safety and efficacy to the satisfaction of the FDA or the results are not otherwise viewed positively or if Verdinexor is not otherwise approved by the FDA for the indication with respect to which we are submitting an application, 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.

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 loss was $33.9 million for the year ended December 31, 2013. As of December 31, 2013, we had an accumulated deficit of $62.6 million. 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 and our initial public offering, or IPO. We have devoted substantially all of our efforts to research and development. Our lead drug candidate, Selinexor (KPT-330), is in clinical development and our other drug candidates for the treatment of human disease 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;

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

ultimately 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;

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 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 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.

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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 and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into early 2016. Our future capital requirements will depend on many factors, including:

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

Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for 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.

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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 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 further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be compromised by economic downturns, a volatile business environment and unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, 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 these 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 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 the development, marketing and/or commercialization of our drug candidates. For example, while we currently plan to conduct three registration-directed clinical trials of Selinexor and make regulatory filings in North America and 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. 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

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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;
- 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.

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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.

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

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the rights, integrity and confidentiality of trial participants are protected. The European Medicines Agency and Health Canada also require 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.

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.

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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. To date, we have obtained starting materials for our supply of the current good manufacturing practices, or cGMP, bulk drug substance for our drug candidates from one third-party manufacturer. We have engaged a separate third-party manufacturer for fill-and-finish services. We do not have a long term supply agreement with either 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 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. We do not currently have arrangements in place for redundant supply or a second source for cGMP bulk drug substance or fill-and-finish services. If our current contract manufacturers cannot perform as agreed, we may be required to replace those manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our drug candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

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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.

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

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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 may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide 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 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.

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

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

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

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to the United States Patent and Trademark Office, or USPTO, and various foreign patent offices at various points over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we rely on our outside counsel to pay these fees when due. Additionally, the USPTO and various foreign patent offices require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply with such provisions, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with rules applicable to the particular jurisdiction. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If such an event were to occur, it could have a material adverse effect on our business.

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

Depending upon the timing, duration and conditions of FDA marketing approval, if any, of our drug candidates, one or more of our U.S. patents may be eligible for patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman

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Amendments. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a 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.

In the United States, only a single patent can be extended for each FDA approval, and any patent can be extended only once, 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.

Our trademarks are not 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, 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 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

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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 Other Legal Compliance Matters

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

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Failure to obtain marketing approval in international jurisdictions would prevent our drug candidates from being marketed abroad.

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 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.

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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 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;

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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 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

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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.

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

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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.

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.

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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.

If we expand our operations outside of the United States, we must comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the DOJ. The Securities and Exchange Commission, or SEC, is involved with enforcement of the books and records provisions of the FCPA.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we

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expand our presence outside of the United States, it will 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 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.

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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.

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, 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.

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 March 14, 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.

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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.

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

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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 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, only two years of audited financial statements and a correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure, 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

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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; however, we estimate that our incremental costs resulting from operating as a public company may be between $2.0 million and $4.0 million per year. In addition, the rules and regulations applicable to public companies are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 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 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. In the course of the preparation and external audit of our consolidated financial statements, we and our independent registered public accounting firm identified "significant deficiencies" in our internal control over financial reporting related to the lack of sufficient staff in our finance department to segregate accounting duties. A significant deficiency is a deficiency, or combination of deficiencies, in internal control over financial reporting that is less severe than a material weakness, yet important enough to merit attention by those responsible for oversight of a company's financial reporting. Following the identification of these control deficiencies, we took actions and measures to improve our internal control over financial reporting by hiring additional employees and consultants at various appropriate levels. Our remediation efforts may not, however, enable us to avoid material weaknesses or other significant deficiencies in the future. 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

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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. Of the approximately 29.8 million shares of our common stock outstanding as of March 14, 2014, approximately 21.9 million shares are currently subject to restrictions on transfer under 180-day lock-up arrangements with either the underwriters for our IPO or under stock option or restricted stock agreements entered into between us and the holders of those shares. The restrictions under the 180-day lock-up arrangements with the underwriters for our IPO and under such option and restricted stock agreements are due to expire on May 4, 2014, resulting in these shares becoming eligible for public sale on May 5, 2014 if they are registered under the Securities Act of 1933, as amended (the "Securities Act"), or if they qualify for an exemption from registration under the Securities Act, including under Rules 144 or 701.

Moreover, holders of an aggregate of approximately 18.6 million shares of our common stock 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 also intend to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described above.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We occupy approximately 7,743 square feet of office and laboratory space in Natick, Massachusetts under a lease that expires on January 31, 2015. In order to accommodate our expected need for additional office and laboratory space, we intend to enter into an agreement to lease approximately 29,933 square feet of office and laboratory space.

Item 3. Legal Proceedings

We are not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

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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, 2013, as reported on the NASDAQ Global Select Market:

	Year Ended December 31, 2013	
	High	Low
Fourth Quarter (from November 6, 2013)	$ 25.69	$ 15.50

Holders

As of March 14, 2014, there were 43 holders of record of our common stock.

Dividends

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

Stock Performance Graph

The following graph shows a comparison from November 6, 2013, the date on which our common stock first began trading on the NASDAQ Global Select Market, 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, 2013. 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.

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COMPARISON OF CUMULATIVE TOTAL RETURN

Among Karyopharm Therapeutics Inc., the NASDAQ Composite Index,
and the NASDAQ Biotechnology Index

Cumulative Total Return Comparison

	11/6/13	11/30/13	12/31/13
Karyopharm Therapeutics Inc.	**100.00**	**101.50**	**142.80**
NASDAQ Composite	**100.00**	**103.65**	**106.84**
NASDAQ Biotechnology	**100.00**	**107.21**	**108.50**

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 Securities and Exchange Act of 1934, 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 of 1933 or the Securities Exchange Act of 1934, except to the extent we specifically incorporate it by reference into such a filing.

Recent Sales of Unregistered Securities

Set forth below is information regarding our grants of options and issuance of shares of our common stock upon the exercise of options and other issuances by us of shares of our capital stock, in each case during 2013, to the extent such transactions were not registered under the Securities Act of 1933, as amended, which we refer to as the Securities Act. Also included is the consideration, if any, received by us for such shares and options and information relating to the section of the Securities Act, or rule of the Securities and Exchange Commission, under which exemption from registration was claimed. No underwriters were involved in any such issuances.

We issued 44,639,529 shares of our preferred stock in private placements in the year ended December 31, 2013, of which 1,538,461 and 6,100,000 shares were issued related to the preferred stock subscription purchased during the years ended December 31, 2012 and 2011, respectively. The Company sold these shares with prices ranging from $1.00 per share to $2.20 per share with aggregate proceeds to us of $72.7 million, $2.0 and $7.0 million for the years ended December 31, 2013, 2012 and 2011, respectively. These shares were issued and sold pursuant to either Regulation D or Regulation S,

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each promulgated under the Securities Act. In November 2013, upon the closing of our initial public offering, or IPO, all shares of our then-outstanding preferred stock, including the shares described in this paragraph, were automatically converted into shares of our common stock. The common stock was issued pursuant to the exemption from the registration requirements of the Securities Act provided by Section 3(a)(9) or Section 4(2) of the Securities Act.

In July 2013, we issued an aggregate of 12,121 shares of our common stock to the holders of our special participation stock, in connection with the election of the holders of a majority of such shares of special participation stock to convert all outstanding shares of special participation stock into common stock. The common stock was issued pursuant to the exemption from the registration requirements of the Securities Act provided by Section 3(a)(9) of the Securities Act.

Between January 1, 2013 and December 31, 2013, we granted options to purchase an aggregate of 1,914,195 shares of our common stock, with exercise prices ranging from $1.49 per share to $23.66 per share, to employees, consultants and directors pursuant to our 2010 Stock Incentive Plan and our 2013 Stock Incentive Plan. Between January 1, 2013 and December 31, 2013, we issued an aggregate of 79,122 shares of common stock upon the exercise of options for aggregate consideration of $34,000. The securities described in this paragraph were issued pursuant to written compensatory plans or arrangements with our employees, consultants, and directors in reliance upon the exemption from the registration requirements of the Securities Act provided by Rule 701 promulgated under the Securities Act. All recipients either received adequate information about us or had access, through employment or other relationships, to such information.

Use of Proceeds from Initial Public Offering

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 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, 2013, we have used approximately $5.8 million of such net offering proceeds to fund the continued clinical development of our lead drug candidate, Selinexor (KPT-330), the preclinical development of our drug candidates for anti-inflammatory, viral and wound-healing indications, the discovery, research, preclinical development and clinical trials 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 and prime money market funds. 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.

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Item 6. Selected Financial Data

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

	Years Ended December 31,			Period from December 22, 2008 (Date of Inception) to December 31,
	2013	2012	2011	2013
	(in thousands, except share and per share data)			
Consolidated Statement of Operations Data:				
Contract and grant revenue	$ 387	$ 634	$ 152	$ 1,266
Operating expenses:				
Research and development	28,452	14,095	8,623	52,835
General and administrative	5,885	2,429	1,840	10,817
Total operating expenses	34,337	16,524	10,463	63,652
Loss from operations	(33,950)	(15,890)	(10,311)	(62,386)
Interest income (expense), net	3	2		(183)
Net loss	$ (33,947)	$ (15,888)	$ (10,311)	$ (62,569)
Net loss per share applicable to common stockholders basic and diluted	$ (5.59)	$ (8.95)	$ (10.27)	$ (35.00)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	6,067,679	1,775,323	1,004,144	1,787,668

	As of December 31,		
	2013	2012	2011
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash and cash equivalents	$ 155,974	$ 391	$ 6,512

Working capital	154,664	(976)	4,749
Total assets	158,226	1,311	7,224
Total preferred stock and preferred stock subscription		27,258	17,758
Total stockholders' equity (deficit)	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 240 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 8-12 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.

Since inception, we have incurred significant operating losses. Our net loss was $33.9 million, $15.9 million and $10.3 million for the years ended December 31, 2013, 2012 and 2011, respectively. As of December 31, 2013, we had an accumulated deficit of $62.6 million. 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;
- ultimately 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;
- 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.

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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.

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, or information provided to us by our vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are 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. We expect to track specific project costs when additional drug candidates 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;
- 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;

launching commercial sales of the drugs, if and when approved, whether alone or in collaboration with others; and

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maintaining a continued acceptable safety profile of the drugs following approval.

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

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

General and Administrative Expenses

General and administrative expenses consist primarily of salaries 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. Additionally, we anticipate that the increased costs associated with being a public company will include expenses related to services associated with maintaining compliance with exchange listing and Securities and Exchange Commission requirements, insurance, and investor relations costs.

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.

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Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include fees paid to contract research organizations, 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.

Stock-based Compensation

Since our initial public offering, the exercise price per share of all options grants has been set at the closing price of our common stock on the NASDAQ Global Select Market on the applicable date of grant, which our board of directors believes represents the fair value of our common stock.

Prior to becoming a public company in November 2013, we utilized significant estimates and assumptions in determining the fair value of our common stock. We granted stock options at exercise prices not less than the fair value of our common stock as determined by the board of directors, with input from management. The board of directors determined the estimated fair market value of our common stock based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry and prices at which we sold shares of convertible preferred stock, the superior rights and preferences of securities senior to our common stock at the time and the likelihood of achieving a liquidity event, such as an initial public offering.

Prior to becoming a public company, we periodically determined for financial reporting purposes the estimated per share fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, also known as the Practice Aid. In conducting the contemporaneous valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects and operating performance

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at each valuation date. Within the contemporaneous valuations performed, a range of factors, assumptions and methodologies were used. The significant factors included:

- the prices of our preferred stock sold to or exchanged between outside investors in arm's length transactions, and the rights, preferences and privileges of our preferred stock as compared to those of our common stock, including the liquidation preferences of our preferred stock;
- our results of operations, financial position and the status of research and development efforts;
- the composition of, and changes to, our management team and board of directors;
- the lack of liquidity of our common stock as a private company;
- our stage of development and business strategy and the material risks related to our business and industry;
- the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies;
- any external market conditions affecting the life sciences and biotechnology industry sectors;
- the likelihood of achieving a liquidity event for the holders of our common stock and stock options, such as an initial public offering, or a sale of our company, given prevailing market conditions; and
- the state of the initial public offering market for similarly-situated privately-held biotechnology companies.

The dates of our contemporaneous valuations have not always coincided with the dates of our option grants. In determining the exercise prices of option grants, our board of directors considered, among other things, the most recent contemporaneous valuations of our common stock and our assessment of additional objective and subjective factors we believed were relevant as of the grant date. The additional factors considered when determining any changes in fair value between the most recent contemporaneous valuation and the grant dates included, when available, the prices paid in recent transactions involving our equity securities, as well as our stage of development, our operating and financial performance and current business conditions.

In July 2013, based on our review of overall market conditions and the improving market for biopharmaceutical initial public offerings, our board of directors determined that a significant shift was occurring with respect to the valuation we could achieve in an initial public offering and directed our management to begin the process of preparing our company for an initial public offering. We selected underwriters and held an organizational meeting in August 2013. We believe these events increased the probability of an initial public offering scenario and therefore, in connection with the preparation of our consolidated financial statements at such time, we re-assessed the fair value of our common stock for financial reporting purposes at interim dates between the contemporaneous valuations where there were stock option grants.

On October 23, 2013, the pricing committee of our board of directors determined the estimated price range for our initial public offering, after consultation with the underwriters. The estimated price range that was determined by the pricing committee of our board of directors implied a higher initial public offering valuation than we used in our contemporaneous common stock valuations. In connection with the process of determining the estimated price range, we re-assessed the fair value of our common stock for financial reporting purposes through additional retrospective valuations.

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 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

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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 fair value of 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 highly subjective 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 similar 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, whereby the expected term equals the average of the vesting term and the original contractual term of the option. For non-employee stock options, we utilize the contractual term of the option. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. We have not paid and do not anticipate paying cash dividends on our shares of common stock; therefore, the expected dividend yield is assumed to be zero.

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 are ultimately expected to vest.

We have computed the fair value of employee and non-employee stock options at date of grant using the following assumptions:

	Year Ended December 31,		
	2013	**2012**	**2011**
Expected volatility	85% 93%	79% 92%	78% 79%
Expected term (in years)	6.25 10	6.25 10	6.25 10
Risk-free interest rate	1.07% 3.01%	0.85% 1.76%	1.18% 2.62%
Expected dividend yield	0.0%	0.0%	0.0%

The weighted average grant date fair value per share was $11.09 for options granted during the year ended December 31, 2013, $1.19 for options granted during the year ended December 31, 2012 and $0.10 for options granted during the year ended December 31, 2011.

We recognized total stock-based compensation expense of approximately $3.8 million during the year ended December 31, 2013, $653,000 during the year ended December 31, 2012 and $24,000 during the year ended December 31, 2011.

We had total unrecognized compensation cost related to unvested share based compensation arrangements of $21.2 million as of December 31, 2013 and $731,000 as of December 31, 2012. We expect to recognize this cost as compensation expense over the weighted average remaining service period of approximately 3.7 years.

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Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2013, 2012 and 2011:

	Years Ended December 31,		
	2013	2012	2011
	(in thousands)		
Contract and grant revenue	$ 387	$ 634	$ 152
Operating expenses:			
Research and development	28,452	14,095	8,623
General and administrative	5,885	2,429	1,840
Loss from operations	(33,950)	(15,890)	(10,311)
Interest income	3	2	
Net loss	$ (33,947)	$ (15,888)	$ (10,311)

Comparison of Years Ended December 31, 2013 and 2012

Contract and Grant Revenue. Contract and grant revenue decreased by $247,000 to $387,000 in 2013 from $634,000 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 $447,000 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 $546,000 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 $1.1 million in personnel costs, primarily due to increased headcount and an increase of $623,000 in stock-based compensation expense related to equity grants to personnel,

an increase of $725,000 in professional fees, primarily related to higher corporate legal fees and audit fees,

an increase of $138,000 in insurance expense, primarily due our becoming a publicly traded company, and

an increase of $108,000 in travel expenses.

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Comparison of Years Ended December 31, 2012 and 2011

Contract and Grant Revenue. Contract and grant revenue increased by $482,000 to $634,000 in 2012 from $152,000 in 2011. The increase in revenue was the result of a full year of revenue recognized in 2012 associated with a grant.

Research and Development Expense. Research and development expense increased by $5.5 million to $14.1 million in 2012 from $8.6 million in 2011. The $5.5 million increase is primarily related to:

- an increase of $2.8 million in clinical trial costs, including a $1.6 million increase in the cost of the active pharmaceutical ingredient and finished drug product,
- an increase of $966,000 in consulting fees, including a $536,000 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 $669,000 in personnel costs, primarily due to increased headcount,
- an increase of $663,000 in collaboration expense, and
- an increase of $586,000 in discovery work, including preclinical studies and screening, which reflects a $371,000 decrease in outsourced medicinal chemistry.

These increases are partially offset by a $373,000 decrease in toxicology and efficacy studies.

General and Administrative Expense. General and administrative expense increased by $589,000 to $2.4 million for 2012 from $1.8 million for 2011. The $589,000 increase is primarily related to:

- an increase of $324,000 in professional fees, primarily related to higher legal fees related to protecting our intellectual property, as well as higher corporate legal fees and audit fees,
- an increase of $80,000 in personnel costs, primarily due to higher bonuses,
- an increase of $57,000 in occupancy expenses due to higher rent expense, and
- an increase of $57,000 in consulting fees, primarily related to business development, investor relations and financial services.

Liquidity and Capital Resources

To date, we have not generated any material revenues. We have financed our operations to date primarily through private placements of our preferred stock and proceeds from our initial public offering. As of December 31, 2013, we had $156.0 million in cash and cash equivalents. As of December 31, 2013, we had received $98.8 million in proceeds from the sale and issuance of preferred stock and $113.2 million in net proceeds from our initial public offering. We expect that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into early 2016.

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Cash flows

The following table provides information regarding our cash flows:

	Years Ended December 31,		
	2013	2012	2011
	(in thousands)		
Net cash used in operating activities	$ (30,290)	$ (15,509)	$ (8,549)
Net cash used in investing activities	(57)	(121)	(376)
Net cash provided by financing activities	185,930	9,509	11,992
Net increase (decrease) in cash and cash equivalents	$ 155,583	$ (6,121)	$ 3,067

Net Cash Used in Operating Activities

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.

Net cash used in operating activities was $15.5 million for the year ended December 31, 2012 compared to $8.5 million for the year ended December 31, 2011. The increase in cash used in operating activities during the year ended December 31, 2012 was driven primarily by an increase in our net loss and by changes in components of working capital, including a decrease in accounts payable and accrued expenses.

Net Cash Used in Investing Activities

Net cash used in investing activities was $57,000 during the year ended December 31, 2013 compared to $121,000 during the year ended December 31, 2012. The cash used in investing activities was for the purchase of property and equipment.

Net cash used in investing activities was $121,000 during the year ended December 31, 2012 compared to $376,000 during the year ended December 31, 2011. 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 $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 the proceeds from the sale of preferred stock and proceeds from our initial public offering.

Net cash provided by financing activities was $9.5 million during the year ended December 31, 2012 compared to $12.0 million during the year ended December 31, 2011. The cash provided by financing activities for both periods was primarily from proceeds from the sale of preferred stock and issuance of the preferred stock subscriptions.

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

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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 and cash equivalents will enable us to fund our current operating plan and capital expenditure requirements into early 2016. Our future capital requirements will depend on many factors, including:

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

Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for 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.

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Contractual Obligations

As of December 31, 2013, we had the following contractual obligations:

	Payments Due by Period			
Contractual Obligations	**Total**	**2014**	**2015**	**2016 and beyond**
		(in thousands)		
Operating lease obligations(1)	$ 106	$ 98	$ 8	
Purchase obligations(2)				
Total contractual cash obligations	$ 106	$ 98	$ 8	

(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 million grant, all of which has been paid to us based on our achievement of specified milestones. We own all inventions and other intellectual property that arose or will arise from the conduct of the research program, which we refer to as program inventions and program intellectual property, respectively.

If we, our affiliates, licensees or transferees commercialize products incorporating a program invention or program intellectual property, which we call research program products, we would be obligated to pay to MMRF mid-single-digit royalties as a percentage of worldwide net sales of research program products, including Selinexor, sold by us, our affiliates, licensees or transferees. If we out-license rights to a research program product, we are obligated to pay MMRF a percentage of certain payments we receive from our licensee for the grant of such rights. If we sell all or substantially all of our assets to one or more third parties who were not our stockholders on the effective date of the agreement, or if one or more third parties acquire more than fifty percent of our equity and payments are made directly to our stockholders for the sale of their shares of our stock, each of which we call a change of control, we will be obligated to pay to MMRF a percentage of the value we or our shareholders receive in connection with such change of control. The maximum aggregate amount we may be obligated to pay to MMRF for royalties, out-licensing our rights or as a result of a change of control is $6 million.

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

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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.

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, 2013 and 2012, we had cash and cash equivalents of $156.0 million and $391,000, 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, particularly because our investments are in cash and cash equivalents. Due to the short-term duration of our investment portfolio 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 investment portfolio.

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 report of our independent registered public accounting firm, appear on pages 99 through 123 of this Annual Report on Form 10-K.

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

There have been no disagreements with our independent accountants on accounting and financial disclosure matters.

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 Securities Exchange Act of 1934, as amended (the "Exchange Act") is recorded, processed, summarized and reported within the time periods specified in the rules and forms prescribed by the Securities and Exchange Commission and is accumulated and communicated to management, including the principal executive officer (our Chief Executive Officer) and principal financial officer (our Senior Vice President, Finance and Administration), to allow timely decisions regarding required disclosure.

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

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disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2013.

Management's Annual Report on Internal Control Over Financial Reporting

This report does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

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, 2013 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 2014 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2014 Proxy Statement. We expect to file our 2014 Proxy Statement with the SEC no later than April 30, 2014.

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 2014 Proxy Statement and is incorporated herein by reference.

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

Karyopharm Therapeutics Inc.
Attention: Investor Relations
2 Mercer Road
Natick, MA 01760

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 2014 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 2014 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 2014 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 2014 Proxy Statement and is incorporated herein by reference.

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PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements

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

(a)(2) Financial Statement Schedules

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

(a)(3) Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the 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 sheets of Karyopharm Therapeutics Inc. and subsidiaries (a development stage company) (the "Company") as of December 31, 2013 and 2012, and the related consolidated statements of operations, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2013, and for the period from December 22, 2008 (date of inception) through December 31, 2013. 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. and subsidiaries as of December 31, 2013 and 2012, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2013, and from December 22, 2008 (date of inception) through December 31, 2013, in conformity with U.S. generally accepted accounting principles.

/s/ McGladrey LLP

Boston, Massachusetts
March 21, 2014

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Karyopharm Therapeutics Inc.
(A Development Stage Company)

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2013	December 31, 2012
ASSETS		
Current assets:		
Cash and cash equivalents (NPM restricted December 31, 2012 $12)	$ 155,974	$ 391
Prepaid expenses and other current assets (NPM restricted December 31, 2012 $485)	1,982	563
Total current assets	157,956	954
Property and equipment, net	240	327
Other assets	30	30
Total assets	$ 158,226	$ 1,311
LIABILITIES, CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable (NPM restricted December 31, 2012 $499)	$ 1,740	$ 1,076
Accrued expenses (NPM restricted December 31, 2012 $312)	1,168	764
Deferred revenue	79	66
Other liabilities	305	24
Total current liabilities	3,292	1,930
Commitments and contingencies (Note 8)		
Preferred stock subscription		8,980
Convertible preferred stock		18,278
		27,258
Stockholders' equity (deficit):		
Common stock, $0.0001 par value; 100,000,000 and 35,000,000 shares authorized at December 31, 2013 and 2012, respectively; 29,587,258 and 2,123,388 shares issued and outstanding at December 31, 2013 and 2012, respectively	3	
Preferred stock, $0.0001 par value; 5,000,000 and no shares authorized at December 31, 2013 and 2012, respectively; no shares issued and outstanding		

Additional paid-in capital	217,500	745
Deficit accumulated during the development stage	(62,569)	(28,622)
Total stockholders' equity (deficit)	154,934	(27,877)
Total liabilities convertible preferred stock and stockholders' equity (deficit)	$ 158,226	$ 1,311

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

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Karyopharm Therapeutics Inc.
(A Development Stage Company)

Consolidated Statements of Operations

(in thousands, except share and per share data)

	For the Years Ended December 31,			Period from December 22, 2008 (date of inception) to December 31, 2013
	2013	2012	2011	
Contract and grant revenue	$ 387	$ 634	$ 152	$ 1,266
Operating expenses:				
Research and development	28,452	14,095	8,623	52,835
General and administrative	5,885	2,429	1,840	10,817
Total operating expenses	34,337	16,524	10,463	63,652
Loss from operations	(33,950)	(15,890)	(10,311)	(62,386)
Other income (expense):				
Interest income	3	2		5
Interest expense				(188)
Total other income (expense)	3	2		(183)
Net loss	$ (33,947)	$ (15,888)	$ (10,311)	$ (62,569)
Net loss per share applicable to common stockholders-basic and diluted	$ (5.59)	$ (8.95)	$ (10.27)	$ (35.00)
Weighted-average number of common shares outstanding used in net loss per share applicable to common stockholders-basic and diluted	6,067,679	1,775,323	1,004,144	1,787,668

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

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Karyopharm Therapeutics Inc.
(A Development Stage Company)

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

For the Period December 22, 2008 (date of inception) to December 31, 2013

(in thousands, except share and per share data)

	Special Participation Shares		Series A Convertible Preferred Shares		Series A2 Convertible Preferred Shares		Series A2-1 Convertible Preferred Shares		Series A-2 Convertible Preferred Shares		Series B Convertible Preferred Shares		Series B-1 Convertible Preferred Shares		Preferred Stock Subscription	Common Shares		Additional Paid-In Capital	Deficit Accumulated During the Development Stage	Total Shareholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Amount	Shares	Amount			
Balance at December 22, 2008 (date of inception)		$		$		$		$		$		$		$	$		$	$	$	$
Net loss																			(179)	(179)
Balance at December 31, 2009																			(179)	(179)
Proceeds from sale of restricted stock																		1		1
Vesting of restricted stock																578,600				
Issuance of common stock in connection with a service agreement																151,515				
Issuance of Series A convertible preferred stock, net of issuance costs of $160			5,000,000	4,840																
Issuance of special participation stock	10,000																			
Conversion of notes payable into Series A convertible preferred stock			937,500	938																
Stock-based compensation expense																		46		46
Net loss																			(2,244)	(2,244)
Balance at December 31, 2010	10,000		5,937,500	5,778												730,115		47	(2,423)	(2,376)
Issuance of common stock in connection with a service																11,170				

agreement								
Vesting of restricted stock						486,921		
Issuance of Series A convertible preferred stock	5,000,000	5,000						
Proceeds from the sale of Series A-2 convertible preferred stock, net of issuance costs of $35				6,100,000	6,980			
Proceeds from sale of restricted stock to advisors							12	12
Stock-based compensation expense							24	24
Net loss							(10,311)	(10,311)

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Karyopharm Therapeutics Inc.
(A Development Stage Company)

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

For the Period December 22, 2008 (date of inception) to December 31, 2013

(in thousands, except share and per share data)

	Special Participation Shares		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		Series B-1 Convertible Preferred Shares		Preferred Stock Subscription		Common Shares		Deficit Accumulated During the Development Stage	Total Shareholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Additional Paid-In Capital	
Balance at December 31, 2011	10,000		10,937,500	10,778											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			7,500,000	7,500																
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)
Balance at December 31, 2012	10,000		18,437,500	18,278											7,638,461	8,980	2,123,388	745	(28,622)	(27,877)
Issuance of Series A preferred stock			2,500,000	2,500																
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											23,100,000	46,057								
Issuance of Series B-1 preferred stock, net of issuance costs of $123																				