

Karyopharm Therapeutics Inc.  
Form 10-K  
February 28, 2019  
Table of Contents

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

**FORM 10-K**

(Mark One)

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

**For the fiscal year ended: December 31, 2018**

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

**For the transition period from \_\_\_\_\_ to \_\_\_\_\_**

**Commission file number: 001-36167**

**KARYOPHARM THERAPEUTICS INC.**

**(Exact name of registrant as specified in its charter)**

**Delaware** **26-3931704**  
**(State or other jurisdiction of** **(I.R.S. Employer**  
**incorporation or organization)** **Identification No.)**  
**85 Wells Avenue, 2<sup>nd</sup> Floor, Newton, Massachusetts 02459**  
**(Address of principal executive offices) (zip code)**

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

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

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

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

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

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

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

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

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

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

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

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

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 30, 2018 was approximately \$820,964,429. Shares of common stock held by each executive officer and director and by each holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

Number of shares outstanding of the registrant's Common Stock as of February 15, 2019: 60,856,091.

**Documents incorporated by reference:**

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2019 in connection with our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

## TABLE OF CONTENTS

|   | <b>Page No.</b> |
|---|-----------------|
| <u>PART I</u>   | 3               |
| Item 1. <u>Business</u>   | 3               |
| Item 1A. <u>Risk Factors</u>  | 57              |
| Item 1B. <u>Unresolved Staff Comments</u>   | 104             |
| Item 2. <u>Properties</u>   | 104             |
| Item 3. <u>Legal Proceedings</u>  | 105             |
| Item 4. <u>Mine Safety Disclosures</u>  | 105             |
| <u>PART II</u>  | 106             |
| Item 5. <u>Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u> | 106             |
| Item 6. <u>Selected Financial Data</u>  | 108             |
| Item 7. <u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>                        | 108             |
| Item 7A. <u>Quantitative and Qualitative Disclosures about Market Risk</u>  | 122             |
| Item 8. <u>Financial Statements and Supplementary Data</u>  | 123             |
| Item 9A. <u>Controls and Procedures</u>   | 123             |
| Item 9B. <u>Other Information</u>   | 125             |
| <u>PART III</u>   | 126             |
| Item 10. <u>Directors, Executive Officers and Corporate Governance</u>  | 126             |
| Item 11. <u>Executive Compensation</u>  | 126             |
| Item 12. <u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>              | 126             |
| Item 13. <u>Certain Relationships and Related Transactions, and Director Independence</u>                                   | 126             |
| Item 14. <u>Principal Accountant Fees and Services</u>  | 126             |
| <u>PART IV</u>  | 127             |
| Item 15. <u>Exhibits and Financial Statement Schedules</u>  | 127             |
| Item 16. <u>Form 10-K Summary</u>   | 127             |
| <u>SIGNATURES</u>   | 170             |

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**Table of Contents**
**Forward-Looking Information**

*This Annual Report on Form 10-K contains forward-looking statements regarding the expectations of Karyopharm Therapeutics Inc., herein referred to as Karyopharm, the Company, we, , or our, with respect to the possible achievement of discovery and development milestones, our future discovery and development efforts, our collaborations with third parties, our future operating results and financial position, our business strategy, and other objectives for future operations. We often use words such as anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, should, continue, and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug discovery and clinical development activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, dependence on any collaborators, competition, our ability to obtain any necessary financing to conduct our planned activities, and other risk factors. Please refer to the section entitled Risk Factors in Part I of this report for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to update any forward-looking statements.*

**PART I****Item 1. Business****BUSINESS****Overview**

We are a clinical-stage pharmaceutical company focused on the discovery, development and subsequent commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **S**elective **I**nhibitor of **N**uclear **E**xport (SINE) compounds that inhibit the nuclear export protein exportin 1 (XPO1). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. Oral selinexor is being evaluated in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Clinical trials evaluating selinexor include the Phase 2b STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2b SADAL

(**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), the pivotal, randomized Phase 3 BOSTON (**B**ortezomib, **S**elinexor and **D**examethasone) study in multiple myeloma, and the Phase 2/3 SEAL (**S**elinexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

## Table of Contents

During 2018, we reported positive top-line data from the STORM and SADAL studies as well as updated interim data for the STOMP and SEAL studies. As a result of the positive top-line results from the STORM and SADAL studies, we are pursuing or plan to pursue marketing approvals for selinexor in the United States and Europe.

Following the positive outcome from the expanded cohort for the STORM study, in August 2018, we announced the completion of the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. Patients with penta-refractory multiple myeloma have previously received the two proteasome inhibitors (PIs), Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two immunomodulatory drugs (IMiDs), Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI and at least one IMiD, Darzalex®; and their disease has progressed following their most recent therapy. The FDA previously granted orphan drug designation and fast track designation to selinexor for the treatment of patients with penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the Prescription Drug User Fee Act (PDUFA).

We also announced the submission of a Marketing Authorization Application to the European Medicines Agency (EMA) in January 2019 with a request for conditional approval. The EMA's Committee for Medicinal Products for Human Use (CHMP) has granted accelerated assessment for the selinexor Marketing Authorization Application. An accelerated assessment is granted to products deemed by the CHMP to be of major interest for public health and represent therapeutic innovation. Accelerated assessments may reduce the active review time of an MAA from the standard 210 days down to 150 days once it has been validated by the EMA.

On February 26, 2019, the FDA convened its Oncologic Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. The proposed indication discussed at the ODAC meeting was for selinexor in combination with dexamethasone for the treatment of patients with refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

Provided that marketing approval is granted by the FDA, we plan to commercialize selinexor in the United States as a treatment of patients in the approved indication as early as the first half of 2019. We are completing the development of our U.S. commercial capabilities to support a potential launch of selinexor in the United States and recently hired our U.S. sales force and expanded our marketing and market access teams. We will either work with existing and potential partners to establish a commercial infrastructure outside the United States or may, in certain geographies, elect to establish the commercial infrastructure ourselves.

Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients with relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with

stem cell rescue), including chimeric antigen receptor modified T (CAR-T) cell therapy and intend to work with the FDA to determine the appropriate timeline for the submission. In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose



## Table of Contents

chemotherapy with stem cell rescue. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates: our other oral SINE compounds eltanexor (KPT-8602) and verdinexor (KPT-335) as well as our oral dual PAK4/NAMPT inhibitor, KPT-9274. We began clinical testing of eltanexor, a second-generation SINE compound, in late 2015. Our clinical development program for eltanexor includes myelodysplastic syndrome, colorectal cancer, and metastatic castration-resistant prostate cancer. We began clinical testing of KPT-9274 in patients with lymphoma or solid tumors during 2016. Verdinexor is our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications as well as lymphoma in companion animals.

### *Commercial Readiness*

During 2018 and early 2019, in preparation for a potential commercial launch of selinexor in the United States subject to marketing approval by the FDA, we had:

expanded our organization with approximately 90 new employees deployed in customer facing activities, with broad experience and expertise in sales, marketing, patient access and product reimbursement and distribution with a focus on oncology; and

developed our commercial capabilities with implementation of systems and infrastructure to support our commercial sales organization and patient-focused programs and appropriate quality systems and compliance policies, systems and procedures.

Following our discussions with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor, we may re-evaluate the investment in our U.S. commercial capabilities.

### *Summary of Clinical Development*

Oral selinexor is being evaluated in multiple later-phase clinical trials in patients with hematological and solid tumor malignancies, often in the relapsed and/or refractory setting. In general, relapsed disease refers to disease that progresses following the expiration of a specified period of time after discontinuation of therapy and refractory disease refers to disease that progresses while the patient is on therapy or within a specified period of time after discontinuation of therapy. To date, oral selinexor has been administered to patients across company- and investigator-sponsored clinical trials; the vast majority of these patients have very heavily pretreated, relapsed or refractory disease. Evidence of single-agent anti-cancer activity has been observed in many patients and selinexor has been sufficiently well-tolerated to allow several of these patients to remain on therapy for prolonged periods.

During 2018, we reported several important clinical data sets for selinexor and executed on our plan to pursue a clinical development initiative focused on obtaining our first regulatory approval for selinexor in multiple myeloma. This strategy is based on the positive results from our Phase 2b STORM study. The STORM study is a single-arm clinical trial evaluating oral selinexor in combination with standard, low-dose dexamethasone in patients with penta-refractory multiple myeloma. Patients with penta-refractory multiple myeloma have previously received the two PIs, Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two IMiDs, Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI and at least one IMiD, Darzalex®; and their disease has

progressed following their most recent therapy.

Based on the results of the clinical data set for Part 1 of the STORM study, which we reported in 2016, we expanded the STORM study, designated Part 2, which enrolled 122 heavily pretreated patients with penta-refractory multiple myeloma. During 2018, we reported the clinical data set from Part 2 of the STORM

## Table of Contents

study in which selinexor demonstrated a compelling overall response rate, median duration of response and survival rates and a predictable and manageable tolerability profile. We believe the clinical data set from Part 2 of the STORM study supports our request for accelerated approval for selinexor as a new treatment for patients.

In April 2018, the FDA granted fast track designation to selinexor for the treatment of patients with penta-refractory multiple myeloma, which indicates that the cohort of patients evaluated in the STORM study represents an unmet medical need, meaning there is no standard of care therapy known to be effective in this population. In August 2018, we announced the completion of the rolling submission of our NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results from Part 2 of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the PDUFA. We also announced the submission of a Marketing Authorization Application to the EMA in January 2019 with a request for conditional approval. The EMA's CHMP has granted accelerated assessment for the selinexor Marketing Authorization Application.

On February 26, 2019, the FDA convened its ODAC to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

The STOMP study, a multi-arm clinical trial in patients with relapsed/refractory multiple myeloma, is evaluating selinexor and low-dose dexamethasone plus standard therapies, such as Revlimid®, Pomalyst®, Velcade®, Kyprolis® or Darzalex. In addition, in June 2018, we opened an additional arm of the STOMP study evaluating selinexor and low-dose dexamethasone plus Revlimid® in patients with newly diagnosed multiple myeloma in June 2018. We presented updated clinical data from the STOMP study at the American Society of Hematology (ASH) 2018 annual meeting demonstrating that selinexor and low-dose dexamethasone plus Darzalex® or Pomalyst® exhibits high response rates when combined. We also presented updated clinical data at the European Hematology Association (EHA) 2018 annual meeting demonstrating that selinexor and low-dose dexamethasone plus Velcade® exhibited high response rates and further supports the rationale for the ongoing Phase 3 BOSTON study. Data from the selinexor and low-dose dexamethasone plus Velcade® arm of the STOMP study was subsequently published in the journal, *Blood*®, in December 2018. At the ASH 2017 annual meeting, we presented data demonstrating that selinexor and low-dose dexamethasone plus Revlimid® exhibited high response rates. A year earlier at the ASH 2016 annual meeting, preliminary safety and efficacy of selinexor plus Kyprolis® (dosed twice weekly) and dexamethasone in patients with multiple myeloma was presented.

Data from the STOMP study have showed that selinexor plus low-dose dexamethasone and Velcade® demonstrated high disease response rates, including for patients whose disease was previously refractory to PIs including Velcade® and/or Kyprolis®. Based on the positive results from the Velcade® arm of the STOMP study, we are conducting the pivotal Phase 3 BOSTON study in patients with multiple myeloma who have had one to three prior lines of therapy. The BOSTON study is evaluating selinexor plus low-dose dexamethasone and Velcade® compared to low-dose dexamethasone plus Velcade®. For the BOSTON study, we have identified the combination dose of selinexor 100mg orally once weekly plus dexamethasone 20mg orally twice weekly and Velcade® 1.3mg/m<sup>2</sup> subcutaneously once

weekly for 4 of 5 weeks. In January 2019, we announced the completion of enrollment of 364 patients in the study. If successful, the BOSTON study may support regulatory approval for multiple myeloma previously treated with one to three prior lines of the therapy and could potentially serve as a confirmatory study if the STORM study serves as the basis for accelerated and/or conditional approval.

## **Table of Contents**

The SADAL study is an open-label Phase 2b clinical trial evaluating single-agent oral selinexor in patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with stem cell rescue), including CAR-T cell therapy. At the ASH 2018 annual meeting, we presented top-line clinical data from the SADAL study demonstrating that selinexor, when administered as a single agent, is clinically active and capable of producing durable responses associated with prolonged overall survival.

In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients that have relapsed and/or refractory DLBCL and intend to work with the FDA to determine the appropriate timeline for the submission. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

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

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

**BOSTON:** Randomized Phase 3 top-line data at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol;

**SEAL:** Randomized Phase 3 top-line data in 2020; and

**STOMP:** Updated data from study arms at future medical meetings.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates in oncology. We began clinical testing of oral eltanexor (KPT-8602), a second-generation SINE compound, in late 2015. We reported results at the ASH 2017 annual meeting showing good tolerability in patients with relapsed/refractory multiple myeloma, and we expanded clinical development of eltanexor to include myelodysplastic syndrome (MDS), colorectal cancer (CRC), and metastatic castration-resistant prostate cancer (mCRPC). We presented encouraging results from the cohort of patients with mCRC at the 2018 European Society for Medical Oncology (ESMO)

## **Table of Contents**

annual meeting. We began clinical testing of oral KPT-9274, a dual PAK4/NAMPT inhibitor, in patients with lymphoma or solid tumors during 2016, and we reported top-line data at the ESMO 2017 annual meeting showing a manageable safety profile and early signals of antitumor activity. During 2017, we licensed to Anivive Lifesciences (Anivive) exclusive worldwide rights for the development and commercialization of oral verdinexor (KPT-335) for the treatment of cancer in companion animals. Our pipeline of drug candidates in oncology other than selinexor is summarized in the chart below.

In addition to its role in cancer, XPO1 is known to play a role in neurological, inflammatory, viral, wound healing and other diseases. In the hands of academic collaborators, SINE compounds have shown activity in a variety of non-oncology models consistent with the biology of XPO1. In January 2018, we entered into an Asset Purchase Agreement with Biogen MA Inc., a subsidiary of Biogen Inc. (Biogen), pursuant to which Biogen acquired KPT-350, an investigational new drug application-ready, oral SINE compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, as well as certain related assets with an initial focus in amyotrophic lateral sclerosis (ALS). SINE compounds have also demonstrated activity in animal models of viral diseases, certain rare diseases and other indications, and we are continuing to develop programs in these areas largely through academic collaborations and non-dilutive funding opportunities with the intent to out-license these programs for clinical development and future commercialization.

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

Since our inception, we have devoted most of our efforts to research and development, and we have not generated any revenue to date from the commercial sale of any drugs. As of December 31, 2018, we had an accumulated deficit of \$673.7 million. We had net losses of \$178.4 million, \$129.0 million and \$109.6 million for the years ended December 31, 2018, 2017 and 2016, respectively.

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

Certain functions may only occur within a particular location in the cell, so one of the ways a cell regulates the function of a particular protein is by controlling that protein's location within the cell. The nuclear pore is a complex gate between the nucleus and cytoplasm, regulating the import and export of most large molecules, called macromolecules, including many proteins, into and out of the nucleus. In healthy cells, nuclear transport, both into and out of the nucleus, is a normal and regular occurrence that is tightly regulated and requires the presence of specific carrier proteins. XPO1 mediates the export of over 220 mammalian cargo proteins and some

**Table of Contents**

growth-promoting mRNAs. Particularly, XPO1 mediates the transport of the majority of tumor suppressor proteins and appears to be the only mediator of nuclear export for these proteins. Cancer cells have increased levels of XPO1, causing the increased export of these tumor suppressor proteins from the nucleus. Since the tumor suppressor proteins must be located in the nucleus to survey for damage and initiate programmed cell death, or apoptosis, XPO1 overexpression in cancer cells counteracts the genome surveillance process that detects DNA damage which can promote cancer. By blocking XPO1, our SINE compounds inhibit the export of tumor suppressor proteins, leading to their accumulation in the nucleus. Subsequently, the accumulation of tumor suppressor proteins amplifies their natural apoptotic function in cancer cells, but with minimal effects on normal cells. Further, SINE compounds reduce the translation of certain growth-promoting and anti-apoptosis proteins – often called oncoproteins – by inhibiting the XPO1-mediated nuclear to cytoplasmic transport of the mRNAs that code for these proteins. The figure below depicts the process by which our SINE compounds inhibit the XPO1-mediated nuclear export of tumor suppressor proteins and oncoprotein mRNAs.

We believe that the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide novel, oral, targeted therapies that enable tumor suppressor proteins to remain in the nucleus and promote the apoptosis of potentially any type of cancer cell. In multiple cancer types, patient tumor biopsies have confirmed that selinexor treatment induces nuclear localization of tumor suppressor proteins and, subsequently, cancer cell death, or apoptosis. We believe that no currently approved cancer treatments and only one current clinical-stage cancer drug candidate are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. Thus, we believe that selinexor's novel mechanism of action and oral administration and low levels of major organ toxicities observed to date in patients treated with selinexor in clinical trials, along with encouraging efficacy data, support the potential for selinexor's broad use across many cancer types, including both hematological and solid tumor malignancies. Our SINE compounds were the first oral XPO1 inhibitors in clinical development. We own all intellectual property rights related to the compounds that we are developing, including composition of matter and

## **Table of Contents**

method of use patents covering selinexor issued by the U.S. Patent and Trademark Office in 2015 and which provide patent protection through at least 2032, prior to any adjustments or extensions.

## **Our Strategy**

The critical components of our business strategy are to:

***Develop and Seek Regulatory Approval of Selinexor, Our Lead Novel Drug Candidate, in North America and Europe.*** We plan to seek regulatory approvals of selinexor in North America and Europe for each indication in which we receive favorable results in a trial with a survival endpoint that is registration-enabling. We may also seek regulatory approvals where a clinical trial demonstrates significant data in a surrogate endpoint, such as overall response rate, that could allow for accelerated or conditional approval. We or our current or future partners may seek marketing approvals in other geographies as well.

***Maximize the Commercial Value of Selinexor and Our Other Drug Candidates.*** To date, we have entered into several strategic arrangements. In October 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. for the development and commercialization of selinexor and eltanexor for all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the ASEAN countries. In May 2018, we entered into an exclusive license agreement with Antengene Therapeutics Limited (Antengene) under which we granted Antengene exclusive rights to develop and commercialize selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field and verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. We currently hold development, marketing, and commercialization rights for selinexor in all other countries and are developing selinexor and seeking regulatory approval for its use in oncology indications without a collaborator in North America and Europe. During 2018 and early 2019, we worked to develop our U.S. commercial capabilities to support a potential launch of selinexor in the United States, including hiring a U.S. sales force in January 2019. Following our discussions with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor based on the STORM study, we may re-evaluate the investment in our U.S. commercial capabilities. We plan to either work with existing and potential partners to establish a commercial infrastructure outside the United States or may, in certain geographies, elect to establish the commercial infrastructure ourselves.

***Maintain Our Competitive Advantage and Scientific Expertise in the Field of Nuclear Transport.*** To further our understanding of the role nuclear transport plays in the underlying biology of cancer, as well other major diseases, we plan to continue research in the field of nuclear transport and related areas, primarily by fostering relationships with top scientific advisors and physicians. We have taken this approach in the past with KPT-350, an investigational new drug application-ready, oral SINE compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, which Biogen acquired from us in early 2018. We believe that investing in the recruitment of exceptional advisors,



employees, and management is critical to our continued leadership in the nuclear transport field. We are collaborating with leading patient advocacy groups to provide education on the science behind our SINE compounds and to support the development and execution of clinical trials. We have advanced the understanding and potential application of SINE compounds in cancer treatment through a broad range of collaborations with leading institutions engaged in evaluating SINE compounds in clinical trials in the United States, Canada, many European countries, Australia, India, Israel, Singapore and elsewhere.

***Continue Developing our Pipeline of Novel Drug Candidates.*** To date, we have identified several drug candidates: our oral SINE compounds selinexor, eltanexor and verdinexor and our oral dual

## **Table of Contents**

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

***Maximize the Value of Our Other SINE Compounds in Non-Oncology Indications through Collaborations.*** We may seek to enter into global or regional development, marketing, and commercialization collaboration arrangements for our other SINE compounds in non-oncology indications. For example, in May 2018, we licensed the development and commercial rights for verdinexor in the non-oncology field to Antengene in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. As described above, in January 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired KPT-350 as well as certain related assets with an initial focus in amyotrophic lateral sclerosis.

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

Cancer is a disease characterized by unregulated cell growth. Cancer cells develop when DNA inside the nucleus of normal cells accumulates damage in genes that regulate cell growth and survival. In healthy cells, proteins called tumor suppressor proteins help prevent accumulation of DNA damage (mutations, chromosomal translocations and other abnormalities) by monitoring DNA for damage, and if damage is detected, the tumor suppressor proteins direct the cell to attempt to repair it. However, if the DNA damage is too severe, the tumor suppressor proteins direct the cell to die in a process called apoptosis.

Proteins, however, are not made inside the nucleus but rather made outside of the nucleus in an area called the cytoplasm. A membrane, called the nuclear membrane, separates the nucleus from the cytoplasm. All large nuclear proteins (larger than 40kDa), including tumor suppressor proteins, must be transported from the cytoplasm into the nucleus to perform their functions in keeping a cell healthy. Proteins are brought into the nucleus from the cytoplasm through a protein complex embedded in the nuclear membrane called the nuclear pore. The nuclear pore works like a gate through which large molecules, including many other proteins, enter and exit the nucleus. When molecules enter the nucleus from the cytoplasm, the process is called import, and when molecules exit from the nucleus to the cytoplasm, the process is called export. The import and export of most proteins and other large molecules between the nucleus and cytoplasm require specific carrier proteins to chaperone their cargo molecules through the nuclear pore complex. Carrier proteins which mediate the import of macromolecules into the nucleus are called importins, and those which mediate the export of macromolecules out of the nucleus are called exportins.

Eight exportins have been identified in human cells. One such export carrier protein was discovered in 1999 and is called exportin 1 (XPO1 or CRM1). XPO1 helps export over 220 cargo proteins. In particular, XPO1 appears to be the sole exporter for most of the tumor suppressor proteins including p53, p21, p27, APC, FOXO, pRB and survivin. In addition to exporting tumor suppressor proteins out of the nucleus, XPO1 mediates the nuclear export of a protein called eukaryotic initiation factor 4E (eIF4E), also called the mRNA cap binding protein. eIF4E binds to the mRNAs for many growth-regulating proteins, including c-myc, bcl-2, bcl-6, Atk1, hDM2 and cyclin D. eIF4E depends on XPO1 to help carry these growth-promoting mRNAs from the nucleus into the cytoplasm where the mRNAs are efficiently translated into proteins. XPO1 also exports the anti-inflammatory protein IκB, which inhibits a protein called NF-κB. NF-κB is found in the nucleus of most cancer cells and plays a role in cancer metastasis and chemotherapy resistance, as well as in many inflammatory and autoimmune diseases. By exporting IκB out of the nucleus, XPO1 augments NF-κB activity.

XPO1 levels are reported to be elevated in nearly all cancer cells when compared to their healthy cell counterparts. Therefore, these elevated levels of XPO1 in cancer cells mediate the rapid export of tumor suppressor proteins as well as I $\kappa$ B and eIF4E out of the nucleus. When compared to healthy cells, the increased export of tumor suppressor proteins in cancer cells may lead to reduced monitoring for DNA damage, the normal

## **Table of Contents**

triggering of apoptosis and increased NF- $\kappa$ B activity. Higher levels of XPO1 expression in cancer cells is also generally correlated with resistance to chemotherapy and poor prognosis of patients.

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

### **XPO1 Mediation of Nuclear Transport**

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

Our lead drug candidates are first-in-class, oral, **Selective Inhibitor of Nuclear Export (SINE)** compounds. SINE compounds inhibit XPO1-mediated nuclear export by strongly, yet reversibly, binding to the XPO1 cargo binding site, effectively blocking the XPO1-cargo protein interaction. The transient XPO1 inhibition period that we have observed to date with our SINE compounds appears to be sufficient for elevation of tumor suppressor protein levels and I $\kappa$ B in the nucleus. Accumulation of tumor suppressor proteins in the nucleus of cancer cells allows them to perform their normal role of detecting DNA damage, thereby inhibiting a cancer cell's ability to divide and promoting apoptosis. Healthy cells also accumulate tumor suppressor proteins in the presence of a

**Table of Contents**

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

**Transient XPO1 Inhibition by SINE Compounds**

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

**Our Initial Indication: Cancer**

Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly one in six deaths is due to cancer. The American Cancer Society estimates that in the United States in 2019, approximately 1.8 million new cancer cases will be diagnosed and approximately 610,000 people will die of cancer. The International Agency for Research on Cancer projects that in 2030, 21.7 million people will be diagnosed with cancer, and 13 million people will die of cancer worldwide, as compared to 14.1 million new cancer diagnoses in 2012 and 8.8 million cancer deaths worldwide in 2015.

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

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**Table of Contents**

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, which target specific biological molecules in the human body that play a role in the rapid cell growth and spread of cancer. Targeted therapeutics are designed specifically to exploit vulnerabilities in cancer cells to improve efficacy, and to minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of a genetic alteration more often found in cancer cells than in healthy cells or attack a target that cancer cells are more dependent on for their growth than are healthy cells.

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

**Our Oncology Drug Candidates*****Selinexor (KPT-330)***

Selinexor is being evaluated in multiple later phase clinical trials in patients with hematological malignancies and solid tumors, often in the relapsed and/or refractory setting. Anti-cancer activity has been observed with tumor reductions and durable disease control across many hematologic malignancies and solid tumors.

In our lead hematologic indication of relapsed or refractory multiple myeloma, selinexor has demonstrated encouraging response rates, including a 26.2% response rate in patients with penta-refractory disease. In clinical trials when used in combination with other anti-myeloma agents, including Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade® (bortezomib) and Darzalex® (daratumumab), selinexor has generated response rates ranging from 50% to 92%. Based on the top-line data presented from our Phase 2b SADAL study, which evaluated patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), our next lead indication, selinexor has demonstrated a response rate of 29.6%, with a response rate of 34% in germinal center (GCB) subtype and a response rate of 21% in non-GCB subtypes of the disease. In addition, there were five patients in the SADAL study whose disease subtype was unable to be classified, and four of these patients experienced a partial response while on selinexor therapy. In liposarcoma, our lead solid tumor indication, patients treated with selinexor achieved progression-free survival of 5.5 months versus 2.7 months for placebo-treated patients, achieving a hazard ratio of 0.67, which represents a 33% reduction in the risk of disease progression or death.

To date, the most commonly reported adverse events (AEs) are predictable in the patient populations being studied and have been generally reversible and/or manageable with standard supportive care and/or dose modification. These AEs often decrease over time and are consistent with those previously reported by patients in our initial clinical trials. A preliminary analysis of safety and tolerability of selinexor was performed on unaudited AE data for 1,672 patients

enrolled in our company-sponsored hematological malignancy and solid tumor clinical trials as of the data cutoff point of March 31, 2018. Overall, the most commonly reported

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## **Table of Contents**

selinexor-related AEs in ongoing clinical studies were generally low-grade and included nausea (66.3%), fatigue (61.4%), anorexia (53.3%), thrombocytopenia (50.1%), anemia (41.8%), vomiting (40.1%), and diarrhea (36.1%). Thrombocytopenia, the most common hematologic treatment-related AE, was reported among 50.1% of patients, and approximately half of these were Grades 3 to 4. The dosing regimens used in our key clinical trials, including BOSTON, STORM, STOMP, SADAL and SEAL, have shown predictable and manageable tolerability, particularly when used once weekly in combination regimens. In certain studies, the AEs reported from treatment arms evaluating selinexor and dexamethasone in combination with other antimyeloma agents were similar to, or reduced, compared to selinexor and dexamethasone alone.

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

### *Advanced Hematological Malignancies*

#### **Multiple Myeloma**

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin (M protein) in the serum or urine, bone disease, kidney disease and immunodeficiency. It is more common in elderly patients, with a median age at diagnosis of 65-70 years. In the United States, the American Cancer Society has estimated that there would be approximately 32,000 new cases of MM diagnosed and approximately 13,000 attributable deaths in 2019. The World Health Organization estimated that approximately 114,000 new cases of MM were diagnosed worldwide in 2012.

The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, which is restricted to healthier, often younger patients, and the subsequent introduction of IMiDs, such as Revlimid® and Pomalyst®, and the PIs Velcade®, Kyprolis® (carfilzomib), and Ninlaro® (ixazomib). Two monoclonal antibodies, Darzalex® and Empliciti® (elotuzumab), have also been approved, as has the histone deacetylase inhibitor Farydak® (panobinostat). The introduction of non-chemotherapeutic agents has led to a significant increase in the survival of patients with MM. Although a wide variety of newly approved or experimental therapies are being used in relapsed and/or refractory patients, including new proteasome inhibitors (oprozomib and marizomib), monoclonal antibodies (with or without toxin conjugates) and cellular therapies like chimeric antigen receptor T-cell (CAR-T) therapy, nearly all patients will eventually relapse and succumb to their disease. With about 13,000 deaths from MM in the United States alone expected to occur, we believe that there remains a need for therapies for patients whose disease has relapsed after, or is refractory to, available therapy.

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

In May 2015, we initiated a Phase 2b clinical trial evaluating oral selinexor and low-dose dexamethasone in patients with heavily pretreated MM. The **Selinexor Treatment of Refractory Myeloma**, or **STORM**, study is a single-arm study evaluating the treatment of relapsed/refractory MM with 80mg of selinexor and 20mg of dexamethasone, each dosed twice weekly. This 40mg per week dose of dexamethasone is considered low dose in the treatment of MM, compared with the high dose dexamethasone which uses three times more of the steroid.



At the ASH 2016 annual meeting, we presented positive results, adjudicated by an independent review committee, from the first cohort of patients enrolled in the STORM study, or Part 1 of the STORM study, which

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**Table of Contents**

included patients with either quad-refractory or penta-refractory multiple myeloma. Patients with quad-refractory disease had previously received prior treatments that included alkylating agents, glucocorticoids, two IMiDs (Revlimid® and Pomalyst®), and two PIs (Velcade® and Kyprolis®), and their disease is refractory to at least one IMiD and at least one PI, and has progressed following their most recent therapy. Patients with penta-refractory multiple myeloma have previously received the two PIs, Velcade® and Kyprolis®, the two IMiDs, Revlimid® and Pomalyst®, and the anti-CD38 monoclonal antibody Darzalex®, as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI, at least one IMiD, Darzalex®; and their disease has progressed following their most recent therapy. Based on the results of the clinical data set for Part 1 of the STORM study, in 2016, we expanded the STORM study, designated Part 2, which enrolled 122 heavily pretreated patients with penta-refractory multiple myeloma.

We presented topline clinical data from Part 2 of the STORM study at the Society of Hematologic Oncology 2018 annual meeting and ASH 2018 annual meeting. Among the 122 patients, the median number of prior treatments regimens was seven and the overall response rate (ORR) as adjudicated by the IRC was 26.2%, which included two stringent complete responses (sCRs), six very good partial responses (VGPRs) and 24 partial responses (PRs). The two sCRs were negative for minimal residual disease, one at the level of  $1 \times 10^{-6}$  and one at  $1 \times 10^{-4}$ . The ORR in patients who had previously received Darzalex® combination therapy (n=86) was 29.1%. The disease control rate for patients who had achieved stable disease or better was 78.7%. Median progression-free survival (PFS) was 3.7 months and the median duration of response (DOR) was 4.4 months. Median overall survival (OS) across the study was 8.6 months. Median OS in the approximately 40% of patients with at least a minimum response on selinexor and dexamethasone was 15.6 months compared to a median OS of 1.7 months in patients whose disease progressed or where response was not evaluable (p<0.0001).

In Part 2 of the STORM study, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms, and were consistent with those previously reported from Part 1 of the STORM study and from other selinexor studies. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (69%), fatigue (56%), anorexia (52%), and weight loss (47%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 treatment-related AEs were thrombocytopenia (54%), anemia (29%), neutropenia (19%) and fatigue (19%). No significant major organ toxicities were observed, and bleeding and infection rates were low. In Part 2 of the STORM study each patient experienced at least one AE, approximately 78.0% of patients received a dose modification of selinexor during the study as a result of AEs and approximately 26.8% of patients discontinued use of selinexor during the study as a result of AEs.

In August 2018, we announced the completion of the rolling submission of our NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the positive outcome from Part 2 of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the PDUFA. We also announced the submission of a Marketing Authorization Application to the EMA in January 2019 with a request for conditional approval. The EMA's CHMP has granted accelerated assessment for the selinexor Marketing Authorization Application. An accelerated assessment is granted to products deemed by the CHMP to be of major interest for public health and represent therapeutic innovation. Accelerated assessments may reduce the active review time of an MAA from the standard 210 days down to 150 days once it has been validated by the EMA.

On February 26, 2019, the FDA convened its ODAC to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. The proposed indication discussed at the ODAC meeting was for selinexor in combination with dexamethasone for the treatment of patients with refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. During the ODAC meeting, the FDA presented issues of concern, including the

limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The

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## Table of Contents

ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

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

Based on preclinical synergy in animal models of MM, in October 2015, we initiated a Phase 1b/2 clinical study of oral selinexor in combination with available treatments for relapsed/refractory MM. In this multi-arm study, **Selinexor and Backbone Treatments of Multiple Myeloma Patients (STOMP)**, we are evaluating the combination of selinexor and low-dose dexamethasone with Revlimid<sup>®</sup>, Pomalyst<sup>®</sup>, Velcade<sup>®</sup>, Kyprolis<sup>®</sup> and Darzalex<sup>®</sup> in patients with previously treated MM. In addition, in June 2018, we opened an additional arm in the STOMP study evaluating selinexor and low-dose dexamethasone plus Revlimid<sup>®</sup> in patients with newly diagnosed multiple myeloma. Each combination is evaluated on a separate arm of the STOMP study and within each combination, two treatment cohorts evaluate once weekly versus twice weekly dosing of selinexor. The primary objectives of the Phase 1 portion are to determine the maximum tolerated dose and recommended Phase 2 and Phase 3 doses for selinexor in these combination therapies. The primary objectives of the Phase 2 portion are to assess preliminary efficacy through ORR, clinical benefit rate and DOR.

### Selinexor in Combination with Velcade<sup>®</sup> and Low-dose Dexamethasone (SVd)

At the EHA 2018 annual meeting, we presented updated results from the selinexor, Velcade<sup>®</sup> and dexamethasone arm of the STOMP study, referred to as SVd. In this study arm, oral selinexor was dose-escalated in once-weekly (80 or 100mg) or twice-weekly (60 or 80mg) regimens. Velcade<sup>®</sup> (1.3mg/m<sup>2</sup> subcutaneously) was administered once-weekly or twice-weekly. Dexamethasone was administered orally either 40mg once-weekly or 20mg twice-weekly. The patients in this cohort were heavily pretreated and many (50%) had MM refractory to a proteasome inhibitor. Across the 42 patients enrolled in the SVd arm as of June 5, 2018, the median number of treatment regimens was three (range of one to 11 prior treatment regimens). Of the overall 40 patients evaluable for efficacy, as of June 5, 2018, 25 responded for an ORR of 63% (one patient having a sCR, four patients having a complete responses (CR), seven patients having a VGPR and 13 patients having a PR). Nearly all patients (38 of 40) had reductions in M-protein, including 33% with a 90% or greater reduction. Among the 19 patients with disease that has relapsed following, or is naïve to, PI therapy, the ORR was 84% and the median PFS was 17.8 months. The results were similar in the subgroup of 18 patients with disease that has relapsed following, or is naïve to, PI therapy and between one and three prior treatment regimens, which is also the patient population closest to those eligible for the BOSTON study. This indication of efficacy in the SVd combination, with weekly Velcade and selinexor, warranted the further evaluation of SVd versus Vd in the BOSTON study given the previously reported ORR of 60-65% and PFS of 7-9 months in the Vd regimen among similar patient populations. Amongst the 21 patients with PI-refractory disease where retreatment with Vd alone would not be expected to induce a significant response, the ORR following SVd treatment was 43%, suggesting that the addition of selinexor to Vd in patients with PI-refractory MM could re-sensitize their disease to a treatment regimen including a PI.

Based on these data, the recommended phase 2 dose regimen for the SVd arm was identified as selinexor (100mg once weekly), Velcade<sup>®</sup> (1.3mg/m<sup>2</sup> once weekly given sub-cutaneously for four of five weeks) and dexamethasone (40mg weekly), which represents 40% less Velcade<sup>®</sup> and 25% less dexamethasone compared to the approved standard Vd regimen. Among the 42 patients evaluable for safety as of the June 5, 2018 data cutoff date, the most common Grade 1/2 AEs were nausea (60%), anorexia (57%), fatigue (45%), diarrhea (40%), vomiting (29%) and weight loss

(24%). Importantly, the reported peripheral neuropathy across all patients was Grade 1/2 and limited to six patients (14%), of which five had prior Velcade® exposure. The most common Grade 3 or higher AEs were thrombocytopenia (45%), neutropenia (26%), fatigue (14%) and anemia (12%).

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**Table of Contents****Selinexor in Combination with Pomalyst® and Low-dose Dexamethasone (SPd)**

At the ASH 2018 annual meeting, we also presented updated results from the selinexor, Pomalyst® and dexamethasone arm of the STOMP study, referred to as SPd. In this study arm, selinexor was dosed orally either once weekly (60 or 80mg) or twice weekly (60 or 80mg) with Pomalyst® (4mg orally, once daily) and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 38 patients enrolled in the SPd arm as of November 15, 2018, the median number of prior treatment regimens was four (range of two to nine prior treatment regimens). Of the overall 34 patients evaluable for efficacy as of November 15, 2018, 17 responded for an ORR of 50% (five patients having a VGPR and 12 patients having a PR). Median PFS for all evaluable patients was 12.2 months, with a follow up of 9.4 months. Responses tended to occur rapidly with a median of one month to onset. In the Pomalyst®-naïve and Revlimid®-relapsed or -refractory population (26 patients), the ORR was 54% and media PFS was 12.2 months. ORR and median PFS in Pomalyst and Revlimid-refractory myeloma were 38% and 5.5 months, respectively.

Among the 38 patients evaluable for safety as of November 15, 2018, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (53%), fatigue (50%) and weight decreased (34%). As expected, the most common treatment-related Grade 3 and 4 AEs were neutropenia (55%), thrombocytopenia (34%), anemia (29%) and leukopenia (18%). There were three Grade 5 treatment-related AEs (febrile neutropenia, intracranial hemorrhage and pneumonia). Based on the tolerability and efficacy data from this study arm, doses of oral selinexor of 60mg and 80mg once weekly are being evaluated in combination with Pomalyst® (3mg orally, once daily) and low dose dexamethasone to determine the recommended Phase 2 dose for this combination regimen.

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

At the ASH 2017 annual meeting, we also presented new data from the selinexor, Revlimid® and dexamethasone arm of the STOMP study, referred to as SRd. In this study arm, oral selinexor was dose-escalated starting at either 60mg once weekly or 60mg twice weekly, with Revlimid® (25mg orally, once daily), and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 19 patients enrolled in the SRd arm as of November 1, 2017, the median number of prior treatment regimens was one (range of one to seven prior treatment regimens). Of the 16 patients evaluable for efficacy, as of November 15, 2017, 13 responded for an ORR of 81% (three patients having a VGPR and 10 patients having a PR). Among the 12 patients in the Revlimid®-naïve population, the ORR was 92%. Median PFS was not reached for either the overall study population or for patients with Revlimid®-naïve disease. The median time on treatment for the overall study population was also not reached.

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

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

At the ASH 2018 annual meeting, we presented new data from the selinexor, Darzalex® and dexamethasone arm of the STOMP study, referred to as SDd. In this study arm, oral selinexor was dose escalated using either 100mg once

weekly or 60mg twice weekly, with Darzalex® (16mg/kg intravenously once weekly) and

**Table of Contents**

dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 28 patients enrolled in the SDd arm as of November 15, 2018, the median number of prior treatment regimens was three (range of two to 10 prior treatment regimens). Of the 26 patients evaluable for efficacy, as of November 15, 2018, 19 responded for an ORR of 79% (seven patients having a VGPR and twelve patients having a PR). The 19 patients that responded were all among the 24 patients in the Darzalex<sup>®</sup>-naïve population. Responses tended to occur rapidly with a median of one month to onset. Median PFS and DOR had not been reached as of the cutoff date. Based on published data, the expected ORR for Darzalex therapy without selinexor in the Darzalex<sup>®</sup>-naïve population is approximately 30%. Thus, the ORR of 79% provides a basis for further evaluation of the SDd combination.

Among the 25 patients evaluable for safety as of November 15, 2018, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (60%), fatigue (48%), diarrhea (32%), vomiting (24%) and anorexia (28%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 treatment-related AEs were thrombocytopenia (44%), anemia (28%), leukopenia (28%) and neutropenia (24%). No Grade 5 AEs were reported. The maximum tolerated dose was not reached. Two dose-limiting toxicities (DLTs) (Grade 3 thrombocytopenia and Grade 2 fatigue) were observed in patients receiving selinexor 60mg twice weekly. No DLTs were reported in the 100mg once weekly cohort. The longest duration of therapy is over 60 weeks. Based on the preliminary tolerability and efficacy data, the recommended phase 2 dose of SDd is selinexor (100mg orally, once weekly), Darzalex<sup>®</sup> (16mg/kg, once weekly) and dexamethasone (40mg orally, once weekly).

**Selinexor in Combination with Kyprolis<sup>®</sup> and Low-dose Dexamethasone (SKd)**

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

**Selinexor in Combination with Revlimid<sup>®</sup> and Low-dose Dexamethasone in Newly Diagnosed Multiple Myeloma (SRd NDMM)**

In June 2018, we initiated an additional arm of the STOMP study evaluating selinexor, Revlimid<sup>®</sup> and dexamethasone in patients with newly diagnosed multiple myeloma (NDMM), referred to as SRd NDMM. Patients eligible for this arm must have symptomatic NDMM requiring systemic therapy. Eligible patients must not have had any prior systemic therapy for NDMM other than corticosteroids. We expect that starting dose of oral selinexor will be 60mg (once weekly) with 40mg of dexamethasone (orally, weekly) and 25mg of Revlimid<sup>®</sup> (orally, once daily).

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

Based on the data from the SVd arm of the STOMP study and following consultation with the FDA and the EMA, we are conducting a pivotal randomized Phase 3 study, known as the BOSTON (**Bortezomib, Selinexor and dexamethasone**) study, which is evaluating SVd compared to standard Velcade<sup>®</sup> and low-dose dexamethasone (Vd) in patients with MM who have had one to three prior lines of therapy. In January 2019, we completed enrollment of the BOSTON study; all enrolled patients have been randomized in a one-to-one fashion to receive either SVd or Vd. For the BOSTON study, we have identified the combination dose of selinexor 100mg orally once weekly plus dexamethasone 20mg orally twice weekly and Velcade<sup>®</sup> 1.3mg/m<sup>2</sup> subcutaneously once weekly for 4 of 5 weeks. The dosing schedule allows for only one scheduled clinic visit per week for patients on the SVd arm with selinexor and



Velcade® to be dosed not more frequently than once per week. Importantly, dosing on the SVd arm will use 40% less Velcade® and 25% less dexamethasone than the Vd arm, which follows the standard Vd dosing schedule. We expect that the reduced exposure provided by the SVd

**Table of Contents**

dosing schedule may significantly reduce common Velcade®- and dexamethasone-related toxicities, which is consistent with the safety data from the 42 patients described above who were treated with SVd on the STOMP study at the recommended dose. For the Vd arm, cross-over to the SVd arm based on objective progression will be permitted. The primary endpoints of the study are ORR and PFS and key secondary endpoints include DOR, OS, and certain other duration and quality of life endpoints. Top-line data from the Phase 3 BOSTON study is anticipated at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

**Non-Hodgkin s Lymphoma**

Non-Hodgkin s Lymphoma (NHL) is a cancer that starts in cells called lymphocytes, which are part of the body s immune system. Lymphocytes are found in the lymph nodes and other lymphoid tissues, such as the spleen and bone marrow, as well as in the blood. DLBCL is the most common and the most aggressive of the different forms of NHL. We estimate that approximately 25,000 patients are diagnosed with DLBCL in the United States each year, with approximately 10,000 deaths per year. Approximately 50% of newly diagnosed patients are currently cured with front-line (typically R-CHOP chemotherapy) and another approximately 10% of patients are cured with second line intensive chemotherapy followed by autologous stem cell transplantation. The remaining patients generally succumb to the disease, with the median overall survival of patients with relapsed or refractory DLBCL after two prior regimens less than one year, and often less than six months. Despite the recent approval of CAR-T therapy, many patients with relapsed/refractory DLBCL are not be medically stable enough to undergo CAR-T therapy and have no new or targeted agents approved for the treatment of their disease.

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

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

In December 2018, we reported updated results from the SADAL study at the ASH 2018 annual meeting. Across the 129 patients enrolled in SADAL as of November 15, 2018, the median number of prior treatment regimens was two (range of two to six prior treatment regimens). Based on the intention-to-treat analysis of the first 115 of 127 patients and as adjudicated by an independent central radiological review committee, as of November 15, 2018, 34 patients responded (11 patients having a CR and 23 patients with a PR) for an ORR of 29.6%. An additional eight patients experienced stable disease (SD), for a disease control rate (DCR) of 36.5%. The median DOR across all patients was 9.2 months and responses tended to occur rapidly. Patients with a CR had a median DOR of 23.0 months and patients with a PR had a median DOR of 7.8 months. As of the data cutoff date of November 15, 2018, seven patients who achieved a CR remained on treatment. In addition, as of the data cutoff date, 12 patients remained on treatment but had not reached their first response assessment and are not included in the top-line efficacy analyses. The median overall survival was 9.1 months for all patients on the study. As of the cutoff date, median survival for the patients with PR or CR was 29.7 months. The median survival for patients with best response of progressive disease or who were not evaluable for response was 3.2 months.

Among the 128 patients evaluated for safety as of the cutoff date, the most common treatment-related AEs were gastrointestinal and constitutional symptoms, along with cytopenias. Most were manageable with dose

**Table of Contents**

modifications and/or supportive care. The most common non-hematologic AEs were nausea (50.0%), fatigue (35.9%), and anorexia (32.0%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 AEs were thrombocytopenia (35.2%), neutropenia (20.3%), and anemia (10.9%) and were generally not associated with clinical sequelae. No significant major organ toxicities were observed, and bleeding and infection rates were low.

Selinexor showed robust, single-agent activity in patients with either GCB or non-GCB subtypes of DLBCL: of the 53 patients with the GCB-subtype, 18 responded (five patients with a CR and 13 patients with a PR) for an ORR of 34.0%. Of the 57 patients with the non-GCB subtype, 12 responded (six patients with a CR and six patients with a PR) for an ORR of 21.1%. In addition, there were five patients enrolled whose subtype was unclassified and 4 of these patients achieved a PR.

In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients that have relapsed and/or refractory DLBCL and intend to work with the FDA to determine the appropriate timeline for the submission. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

**Advanced or Metastatic Solid Tumor Malignancies**

Solid tumors represent the vast majority of cancer incidences. Given the large patient population with solid tumors and the mechanistic activity of selinexor that makes it potentially suitable for treating any type of cancer, we are developing selinexor to potentially play a meaningful role across multiple solid tumor indications, either alone or in combination as a backbone therapy. We have seen encouraging single agent data for selinexor in a variety of solid tumors including PRs and durable SD with disease control greater than three months. Our Phase 1b study in patients with liposarcoma and other sarcomas demonstrated durable SD with single-agent selinexor, and our Phase 2 studies of selinexor in gynecological malignancies and glioblastoma multiforme (GBM) also demonstrated anti-cancer activity and disease control. Given the promising single-agent activity in difficult-to-treat indications and the potential to enhance activity in combination with existing therapies, we plan to further develop selinexor in unmet needs like certain gynecological malignancies or GBM, and to advance combination therapy development with both standard of care and emerging therapies like immune checkpoint inhibitors.

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

Liposarcoma represents an area of high unmet need with limited treatment options. Liposarcoma arises from fat cells or their precursors and represents up to 18% of all soft tissue sarcoma, or approximately 2,500 new cases per year in the United States. Liposarcoma most commonly occurs in the thigh, behind the knee, the groin, the gluteal area or behind the abdominal cavity. Dedifferentiated liposarcoma is an aggressive form of soft tissue sarcoma that is resistant to both standard chemotherapy and radiation. Liposarcoma has a particularly high rate of recurrence following surgery, especially in cases involving the abdomen. Except for cases that are cured with surgery, most patients with metastatic liposarcoma will succumb to this disease, and novel therapies are needed.

In our Phase 1b trial to evaluate the effects of food and formulation on selinexor pharmacokinetics in patients with soft-tissue or bone sarcoma, 31 of 54 sarcoma patients (57%) experienced SD with single-agent selinexor treatment. Of the 18 patients with liposarcoma, 14 (78%) experienced SD and eight (44%) experienced SD of four months or longer. Fifteen of these 18 patients with liposarcoma had dedifferentiated liposarcoma. Of these 15 patients with dedifferentiated liposarcoma, 13 (87%) experienced SD and seven (47%) experienced SD of four months or longer.

In light of the Phase 1b data, we are conducting the **Selinexor in Advanced Liposarcoma (SEAL)** study, a multi-center, randomized, double-blind, placebo-controlled Phase 2/3 clinical trial evaluating single-agent oral

**Table of Contents**

selinexor in patients with advanced unresectable dedifferentiated liposarcoma who received at least one line of prior systemic therapy. Patients are randomized to receive either 60mg of selinexor or placebo given twice weekly until progression or intolerability. Patients on placebo with confirmed progressive disease are permitted to cross over to the selinexor treatment arm. In June 2018, we reported a successful outcome from the Phase 2 portion of the SEAL study of 56 patients with previously treated, advanced unresectable dedifferentiated liposarcoma. The median number of prior treatment regimens was two (range of two to 10 prior treatment regimens). For the study's primary endpoint, patients treated with selinexor achieved PFS of 5.5 months, compared to 2.7 months for placebo-treated patients with a hazard ratio (HR) of 0.67, representing a 33% reduction in the risk of progression or death. PFS was assessed by an Independent Central Radiological Review (ICRR) based on RECIST v1.1. In this randomized, blinded Phase 2 portion of the study, selinexor demonstrated an expected and manageable safety profile, primarily with nausea, fatigue, anorexia and weight loss, and low levels of Grade 3/4 cytopenias, and no new or unexpected safety signals were identified. The majority of treatment-related AEs were low grade and reversible with dose modifications and/or standard supportive care. The data from the Phase 2 portion of the SEAL study, which is complete, demonstrate that treatment with selinexor improves PFS (RECIST v1.1) and supports the currently ongoing Phase 3 portion of the study using RECIST v1.1 response criteria, and for which top-line data are expected in the first half of 2020.

The Phase 3 portion of the SEAL study, which was originally initiated in North America, is ongoing and has been expanded to include Europe. In this blinded, placebo-controlled Phase 3 study, up to 222 patients are expected to be enrolled and randomized 2:1 to receive either oral selinexor (60mg twice weekly) until disease progression or intolerability, or placebo. Patients whose disease progresses on placebo will be permitted to cross over to the selinexor arm. The primary endpoint of the Phase 3 portion of the study is PFS as assessed by the ICRR based on RECIST v1.1. The Phase 3 study design and primary endpoint of PFS were agreed to by the FDA. Top-line data from the Phase 3 portion of the SEAL study are anticipated in 2020. Assuming a positive outcome, these data are intended to support a NDA for oral selinexor as a potential new treatment for patients with advanced unresectable dedifferentiated liposarcoma.

*SIENDO: Investigator-Sponsored Randomized Phase 3 Trial of Maintenance Selinexor/Placebo After Combination Chemotherapy In Patients with Advanced or Recurrent ENDOmetrial Cancer*

SIENDO is an investigator-sponsored Phase 3 trial of maintenance with selinexor or placebo after combination chemotherapy for patients with advanced or recurrent endometrial cancer. The overall objective is to obtain conclusive evidence of efficacy for maintenance selinexor in patients with advanced or recurrent endometrial cancer. This is a multi-center/multinational trial expected to enroll 192 patients. We expect that top-line data from this study will be presented in 2020.

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

weeks. Fifteen patients remained on single-agent selinexor for greater than 6 months, including 4 patients continuing on treatment for greater than 12 months.

## **Table of Contents**

### *KING: Phase 2 Clinical Trial of Selinexor in Glioblastoma Multiforme*

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

We are evaluating the next steps for continued clinical development of selinexor in GBM.

## **Our Other Pipeline Programs**

### *Eltanexor (KPT-8602)*

Eltanexor is a second-generation SINE compound that, like selinexor, selectively blocks the nuclear export protein XPO1. The mechanism of action for the biological (anti-cancer) activity of eltanexor is believed to be the same as selinexor.

Eltanexor differs from selinexor primarily because it has much lower penetration into the brain in preclinical species, and, therefore, may cause fewer side effects such as nausea, fatigue and anorexia in patients. Following oral administration, animals treated with eltanexor show lower percentage of body weight loss and improved food consumption, as well as less fatigue behavior, in comparison to animals similarly treated with selinexor. This allows more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than is possible with selinexor, which allows for greater indication diversification among our SINE compounds. In many preclinical model systems, the more intensive dosing regimen leads to superior efficacy in comparison to selinexor treatment. As a result, we believe that eltanexor represents a second-generation SINE compound and are evaluating safety, tolerability and efficacy in humans.

We initiated our first-in-humans Phase 1/2 clinical trial for eltanexor in patients with relapsed/refractory multiple myeloma in January 2016. At the ASH 2017 annual meeting, we reported positive data from the ongoing Phase 1/2 study demonstrating good tolerability and promising activity in MM. Using a 3+3 dose escalation design, oral eltanexor (5, 10, 20, 30 and 40mg) was dosed once daily for five days per week or once every other day for three days each week (60mg) for a 28-day cycle. Patients with less than a minimal response after one cycle or partial response after two cycles were permitted to add dexamethasone. Of the 34 evaluable patients, 14 received dexamethasone with their eltanexor regimen from the first day of the first cycle. Deeper and faster responses were observed when dexamethasone was started on Day 1 of Cycle 1 versus a delayed start. As of January 2019, there were two active patients remaining on study. The median time on treatment for the overall study population was greater than 130 days, with a range of 10 to greater than 770 days.

Among the 39 patients evaluable for safety, the most common Grade 1/2 AEs in the MM patient population were nausea (54%), fatigue (46%), anemia (38%), diarrhea (38%), dysgeusia (33%), weight loss (33%) and neutropenia (31%). As expected in this patient population, the most common Grade 3/4 AEs were thrombocytopenia (56%), neutropenia (26%), anemia (15%), leukopenia (15%) and hyponatremia (10%). Importantly, nausea, fatigue, diarrhea and vomiting were nearly all Grade 1, manageable and transient, and bleeding was uncommon. The maximum



tolerated dose was not reached; however, dose escalation was halted as responses were achieved. Based on these data, the recommended phase 2 dose has been established as 20mg eltanexor dosed five times per week with 20mg dexamethasone dosed twice weekly.

This Phase 1/2 study has been expanded to include patients with high risk MDS, metastatic CRC or mCRPC to determine the safety, preliminary efficacy, and recommended phase 2 dose of eltanexor in patients with these

## **Table of Contents**

advanced cancers. These are indications where selinexor and XPO1 inhibition has shown clear activity, but where side effects such as fatigue and anorexia were problematic for patients due to the underlying malignancies.

At the ESMO Congress in October 2018, positive data were reported from the ongoing Phase 1/2 investigator-sponsored study in the dose expansion cohort in patients with heavily pre-treated (median of four prior treatments) mCRC. The presented results showed that 37% of patients experienced disease control at 38 weeks on eltanexor and the median preliminary PFS for all patients in the 30 mg cohort was 3.5 months. Adverse events were generally predictable and manageable. The highest observed treatment-related Grade 3 or higher AEs were hyponatremia (23%), fatigue (20%) and anemia (20%). These preliminary results demonstrated promising efficacy with a median PFS longer than currently available third line therapies and an acceptable safety and tolerability profile.

### ***KPT-9274***

KPT-9274 is a first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of p21-activated kinase 4 (PAK4) and NAMPT (nicotinamide phosphoribosyltransferase; also known as PBEF or visfatin). Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of DNA repair, cell cycle arrest, inhibition of proliferation, and ultimately apoptosis. Normal cells are more resistant to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic rates. Hematologic and solid tumor cells become dependent on both PAK4 and NAMPT pathways and are therefore susceptible to single-agent cytotoxic effect of KPT-9274.

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

NAMPT is a pleiotropic protein with multiple intra- and extra-cellular functions that can be found in complex with PAK4 in the cell. NAMPT is of interest as an oncology target because it catalyzes the rate-limiting step in one of the two intracellular salvage pathways that generate nicotinamide adenine dinucleotide (NAD). NAD is a universal energy- and signal-carrying molecule involved in mitochondrial function and energy metabolism, as well as in DNA repair (through Poly-ADP-Ribose Polymerase, or PARP) and epigenetics (through sirtuins, or SIRT6). An alternate salvage pathway utilizes the rate-limiting enzyme NAPRT1 to convert nicotinic acid or niacin into NAD. NAPRT1 is often silenced through promoter hypermethylation in tumor samples while it remains expressed in normal tissues. Patients that have NAPRT1 negative tumors may be able to benefit from niacin co-dosing to alleviate KPT-9274 adverse effects while maintaining inhibitory activity in their tumors. Therefore, patients can be stratified according to their NAPRT1 tumor status.

KPT-9274 has shown broad evidence of anti-cancer activity against hematological and solid tumor malignant cells while showing minimal toxicity to normal cells in vitro. In mouse xenograft studies, KPT-9274 given orally has shown evidence of anti-cancer activity and tolerability. To our knowledge, we are the only company with an allosteric, PAK4 and/or NAMPT specific inhibitor currently in clinical development.

We initiated a first-in-humans Phase 1 open-label clinical trial evaluating the safety, tolerability, and efficacy of KPT-9274 in patients with advanced solid malignancies or non-Hodgkin's lymphoma. Top-line results from this Phase 1 study were presented in September 2017 at the ESMO annual meeting. Among the 18 patients evaluable for preliminary efficacy, there were six (33%) with SD, the longest for 7.3 months. Tumor reductions (shrinkage of 3.9%, 13.6% and 22.6%) were observed in three out of three patients (100%) with NAPRT1 deficient tumors. Among the 21 patients evaluated for safety, the most common Grade 2 AEs across dose levels were arthralgia (43%), anemia (24%) and fatigue (24%). The most common drug-related Grade 3 or higher AEs across dose levels include anemia (38%)

and fatigue (5%). Gastrointestinal-related AEs were infrequent and low grade. In addition, it was determined that niacin can be safely administered with KPT-9274 and may improve tolerability, particularly with respect to anemia. Dose escalation remains ongoing and further

**Table of Contents**

evaluation of effects in NAPRT1 deficient tumors is planned. Enrollment is planned to continue based on the patients NAPRT1 status in a 2:1 ratio (NAPRT1- : NAPRT1+). These study findings indicate that in patients whose disease has progressed despite most available therapies, KPT-9274 can induce tumor shrinkage and disease stabilization.

***Verdinexor (KPT-335): Oral SINE Compound for Lymphoma in Companion Canines***

We have used spontaneously occurring canine cancers as a surrogate model for human malignancies. It is widely known that canine lymphomas display a comparable genetic profile and respond to chemotherapy in a fashion similar to their human counterparts (human NHL, most closely DLBCL). Lymphomas are one of the most common tumors in pet dogs. Lymphoma in dogs is very aggressive and, without treatment, the tumors are often fatal within weeks. The majority of dog lymphomas are DLBCL and most of the others are T-cell lymphomas. Given the similarities of dog and human lymphomas, prior to initiating clinical trials of selinexor in humans, we investigated verdinexor (KPT-335), a closely-related, orally available SINE compound in pet dogs with lymphomas. We have received a Minor Use / Minor Species (MUMS) designation from the FDA's Center for Veterinary Medicine (CVM) for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in pet dogs with verdinexor.

Several different dog tumor cell lines, including those derived from lymphomas, exhibited growth inhibition and apoptosis in vitro upon exposure to nanomolar concentrations of verdinexor. Data from a Phase 1 clinical trial of verdinexor as well as dose expansion study involving pet dogs with cancer, primarily with lymphoma, show efficacy of verdinexor to treat dogs with lymphoma. Side effects included anorexia, weight loss, vomiting and diarrhea and were manageable with dose modulation and supportive care. We conducted an owner observation-based survey and the data indicated that the overall quality of life did not change significantly in dogs treated with verdinexor. Based on these findings, a Phase 2b clinical trial, intended to support regulatory approval under the MUMS designation in the United States, was performed in 58 pet dogs with either newly-diagnosed or first relapse after chemotherapy lymphomas. In this Phase 2b clinical trial, verdinexor was administered initially at doses ranging from 25mg/m<sup>2</sup> to 30mg/m<sup>2</sup> two or three days per week. Minimal or no supportive care was given. The total CRs and PRs of the 58 dogs was 34%, with one CR and 19 PRs. An additional 33 of 58 dogs (57%) experienced SD for at least four weeks. The median time to disease progression was approximately five weeks, with 20 dogs (34%) remaining on study for longer than eight weeks. A few dogs that received verdinexor in the Phase 1 or 2b studies remained on therapy for longer than eight months. We submitted the safety and effectiveness sections of a New Animal Drug Application for verdinexor to the CVM in December 2013.

In May 2017, we entered into an exclusive licensing agreement with Anivive, a privately-held biotech company focused on innovations in the veterinary drug and bioinformatics space, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In exchange, we received an upfront payment and are eligible to receive future milestone payments and royalties. If approved, we believe that verdinexor would represent the first oral, targeted therapy for the treatment of dog lymphoma.

**Our Non-Oncology Drug Candidates*****Verdinexor (KPT-335): Oral SINE Compound for Viral, Rare Disease and Autoimmune Indications***

Verdinexor (KPT-335) is an oral SINE compound and our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications, in addition to the canine lymphoma program described above. Several autoimmune indications are driven by aberrant pro-inflammatory responses, particularly uncontrolled NF- $\kappa$ B activation. These include systemic lupus erythematosus (SLE), a primary focus of our work with verdinexor. Funded by a grant under the Small Business Innovation Research program, we expect to complete pre-clinical

evaluation of verdinexor as a treatment for SLE by the end of year 2019, when we expect to be in position to file an IND application with the FDA.

## **Table of Contents**

In addition to autoimmune disorders, several viruses exclusively utilize XPO1 to shuttle cargos necessary for viral replication, such as viral and host proteins from the nucleus to the cytoplasm. Due to the stability of host gene targets compared to viruses which rapidly adapt for best fitness in hosts, targeting host genes may offer an approach to limit drug resistance. We intend to extend preclinical research in viruses that may be relevant to patients with compromised immune systems, such as respiratory syncytial virus and cytomegalovirus, along with highly relevant pathogens currently causing outbreaks such as enterovirus 68 (acute flaccid myelitis). We also intend to investigate verdinexor to treat inflammation in virally-suppressed antiretroviral therapy-receiving individuals.

In 2015, we conducted a randomized, double-blind, placebo-controlled, dose-escalating Phase 1 clinical trial of verdinexor in healthy human volunteers in Australia. This study was designed to evaluate the safety and tolerability of verdinexor in healthy adult subjects. Verdinexor was found to be generally safe and well tolerated. Mild to moderate AEs of similar number and grade as placebo were reported, and no serious or severe AEs were observed. We plan to continue to explore strategies to pursue the clinical development of verdinexor as a treatment for viral, inflammatory, and autoimmune indications, including potentially partnering with a collaborator or through government-funded grant or contract opportunities.

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

## **Our Strategic Relationships**

On May 23, 2018, we entered into a license agreement (Antengene Agreement) with Antengene and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People's Republic of China, pursuant to which we granted Antengene exclusive rights to develop and commercialize, at its own cost, selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field, as well as verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. Under the terms of the Antengene Agreement, we received an upfront cash payment of \$11.7 million and are entitled to receive up to \$105.0 million in milestone payments from Antengene if certain development goals are achieved and up to \$45.0 million in milestone payments from Antengene if certain sales milestones are achieved. We are further eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor in China and Macau, and tiered single- to double-digit royalties based on future net sales of KPT-9274 and verdinexor in the licensed territories. Antengene's obligations under the Antengene Agreement have been guaranteed by Antengene Corporation Co. Ltd.

On January 24, 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired exclusive worldwide rights to develop and commercialize our oral SINE compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis. KPT-350 is an IND-ready oral SINE compound with a preclinical data package supporting potential efficacy across a number of neurological, autoimmune and inflammatory conditions. XPO1 mediates the nuclear export of multiple proteins that impact neurological, autoimmune and inflammatory processes. Consequently, inhibition of XPO1 by KPT-350 results in a reduction in autoimmunity and inflammation and an increase in anti-inflammatory and neuroprotective responses. KPT-350 penetrates the blood brain barrier to a greater degree than other SINE compounds. Preclinical data generated largely by external

collaborators show efficacy of KPT-350 and related SINE compounds in animal models of amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injury, epilepsy,

## **Table of Contents**

systemic lupus erythematosus and rheumatoid arthritis. We received a one-time upfront payment of \$10.0 million from Biogen and are eligible to receive additional payments of up to \$207.0 million based on the achievement by Biogen of future specified development and commercial milestones. We are also eligible to receive tiered royalty payments that reach low double digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product or the expiration of specified patent protection for the applicable product, determined on a county-by-country basis.

Effective October 11, 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. (Ono), whereby Ono received rights to develop and commercialize selinexor and eltanexor (KPT-8602), at its own cost and expense, for the diagnosis, treatment and/or prevention of all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and ASEAN countries, which we refer to as the Ono Territory. In exchange, we received a one-time upfront payment of ¥2.5 billion (approximately US\$21.9 million) from Ono and retain all rights to selinexor and eltanexor outside the Ono Territory. We are eligible to receive up to an additional ¥19.2 billion (approximately US\$170.7 million at the exchange rate on the effective date of the agreement) if specified future development and commercial milestones are achieved by Ono. We are also eligible to receive low double-digit royalties based on future net sales of selinexor and eltanexor in the Ono Territory. Ono will have the ability to participate in any global clinical study of selinexor and eltanexor and will bear the cost and expense for patients enrolled in clinical studies in the Ono Territory.

In May 2017, we entered into an exclusive licensing agreement with Anivive, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In exchange, we received an upfront payment of \$1.0 million and a subsequent milestone of \$250,000 and are eligible to receive up to \$43.3 million in future regulatory, clinical and commercial milestone payments, assuming approval in both the United States and the European Union. In addition, Anivive agreed to pay us up to low double-digit royalty payments based on future net sales of verdinexor. If approved, we believe that verdinexor would represent the first oral, targeted therapy for the treatment of dog lymphoma.

## **Intellectual Property**

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

We file patent applications directed to the composition of matter and methods of use and manufacture for our drug candidates. As of February 1, 2019, we were the sole owner of 13 patents in the United States and we had 16 pending patent applications in the United States, 47 granted patents and 117 pending patent applications in foreign jurisdictions. The technology underlying such pending patent applications has been developed by us and was not acquired from any in-licensing agreement.

The intellectual property portfolios for our key drug candidates as of February 1, 2019 are summarized below.



**Selinexor (KPT-330):** Our selinexor patent portfolio covers the composition of matter and methods of use of selinexor, as well as methods of making selinexor, and consists of three issued U.S. patents (one patent is specific to selinexor, and the two other patents cover both selinexor and verdinexor), 19 issued foreign patents, 39 pending foreign patent applications, and two pending U.S. non-provisional application, one directed to polymorphs of selinexor. Any patents that may issue in the United States as part of our selinexor patent portfolio, with the exception of a patent directed to the polymorphs of

## Table of Contents

selinexor, will expire in 2032, absent any terminal disclaimer, patent term adjustment due to administrative delays by the United States Patent and Trademark Office (USPTO) or patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. Any patents that may issue in foreign jurisdictions will likewise expire in 2032. Any patents that may issue in the United States directed to the polymorphs of selinexor will expire in 2035, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patent issued in foreign jurisdictions will likewise expire in 2035.

**Selinexor (Wound Healing):** Our patent portfolio covering selinexor for wound healing, including acute and chronic wounds, burns and scars, covers methods of using selinexor or verdinexor for wound healing, including systemic and topical uses, and consists of one pending U.S. application and one pending European application. Any patents that may issue in the United States will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delay by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in Europe will likewise expire in 2034.

**Verdinexor (KPT-335):** Our selinexor patent portfolio described above, with the exception of the applications directed to polymorphs of selinexor, also covers both the composition of matter and methods of use of verdinexor, as well as methods of making verdinexor. There are four issued U.S. Patents that cover verdinexor. One patent is specific to verdinexor, two patents cover both verdinexor and selinexor (also referenced above with respect to selinexor) and the other covers veterinary uses of verdinexor.

**Eltanexor (KPT-8602):** Our eltanexor patent portfolio covers both the composition of matter and methods of use of eltanexor, and consists of one issued U.S. patent, one pending provisional U.S. patent application, one pending non-provisional U.S. patent application, two issued foreign patents and 23 pending foreign patent applications. Any patents that may issue in the United States as part of our eltanexor patent portfolio, with the exception of a patent based on the pending provisional U.S. patent application, will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2034. Any patents that may issue in the United States based on the pending provisional U.S. patent application will expire in 2039, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2039.

**PAK4/NAMPT Inhibitors:** Our PAK4/NAMPT inhibitors patent portfolio covers both the composition of matter and methods of use of the PAK4/NAMPT inhibitors described therein, such as KPT-9274, and consists of nine patent families with three issued U.S. patent, three issued foreign patents, seven pending U.S. non-provisional patent applications, and 34 pending foreign patent applications in total. Any patents that may issue in the United States based on the pending U.S. non-provisional applications will expire in 2033 for the earliest filed application and 2034, 2035 or 2036 for the remaining applications, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents that may issue based on the pending foreign patent applications will likewise expire in 2033, 2034 or 2036. Foreign patent applications covering the composition of matter and methods of use of KPT-9274 have been filed in 21 countries/regions.

In addition to the patent portfolios covering our key drug candidates, as of February 1, 2019, our patent portfolio also includes four patents (U.S. Patent Nos. 8,513,230, 9,303,000, 9,428,490 and 9,550,757) and 22 granted foreign patents and pending patent applications in the U.S. and foreign jurisdictions relating to other XPO1 inhibitors and their use in targeted therapeutics and biomarkers for XPO1 inhibitors. We also filed three Intent to Use Trademark Applications on August 29, 2013 covering our name, our logo and the two used

## **Table of Contents**

together. Marks for the name and name and logo together were registered in the United States on January 20, 2015 as Registration Nos. 4,676,255 and 4,676,226. The mark for our logo was registered in the United States on February 24, 2015 as Registration No. 4,693,107. We also have registered PORE in the United States for our online portal. As of February 1, 2019, we have pending Intent to Use Trademark Applications in the United States for seven possible drug names for selinexor, and for KARYFORWARD for our financial assistance and charitable services. We have filed applications for all seven selinexor names in sixteen jurisdictions, and we have filed for two of those names in twelve additional jurisdictions. Some of the international filings for the drug names are registered, while some are pending.

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

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our drug candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Our issued patents and any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us. In addition, because of the extensive time required for clinical development and regulatory review of a drug candidate we may develop, it is possible that, before any of our drug candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements with selected consultants, scientific advisors and collaborators requiring assignment of inventions. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through our relationship with a third party.

With respect to our proprietary drug discovery and optimization platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. We anticipate that with respect to this technology platform, these trade secrets and know-how may over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.



## **Table of Contents**

### **Competition**

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any drug candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are several companies developing or marketing treatments for cancer and the other indications on which we currently plan to focus, including major pharmaceutical and biotechnology companies. To our knowledge, only one other company with an XPO1 inhibitor has enrolled patients in clinical trials at the present time. Stemline Therapeutics, Inc. announced in January 2015 that it had exclusively licensed the rights to develop and commercialize SL-801, an oral XPO1 inhibitor, from CanBas Co., Ltd. In December 2015, Stemline announced the opening of its IND and planned initiation of a clinical development program in multiple cancer types. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors.

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 necessary for, our programs.

The key competitive factors affecting the success of any approved oncology drug product, including our drug candidates, if approved, are likely to be their efficacy, safety, convenience and price, the availability of alternative cancer therapies and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs, or commercialize existing drugs in new indications, and those drugs are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic drugs. Generic drugs for the treatment of cancer and the other indications on which we currently plan to initially focus are currently on the market, and additional drugs are expected to become available on a generic basis over the coming years. If we obtain marketing approval for our drug candidates, we expect that they will be priced at a significant premium over generic versions of older chemotherapy agents and other cancer therapies.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our drug candidates may compete with many existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our drug candidates will be complimentary with them. Some of the currently-approved drug therapies are branded and subject to patent protection,

and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely-accepted by physicians, patients and third-party payors.

In addition to currently-marketed therapies, there are also a number of drugs in late stage clinical development to treat cancer and the other indications on which we plan to initially focus. These drugs in

**Table of Contents**

development may provide efficacy, safety, convenience and other benefits that are not provided by currently-marketed therapies. As a result, they may provide significant competition for any of our drug candidates for which we obtain marketing approval.

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

***Multiple Myeloma (MM)***

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

Several other anti-cancer agents are in late-stage development for the treatment of patients with MM, including anti-B cell maturation antigen (BCMA), based CAR-T therapies such as bb2121 (Bluebird Bio/Celgene), JCHARHI25 (Juno Therapeutics/Celgene), P-BCMA-101 (Johnson & Johnson/Poseida Therapeutics), LCAR-B38M (Johnson & Johnson/Legend BioTech) and CART-BCMA (Novartis); monoclonal antibodies such as isatuximab (Sanofi) and Opdivo® (nivolumab, BMS); antibody-drug conjugates such as GSK2857916 (GlaxoSmithKline); bi-specific antibodies such as AMG420 (Amgen), REGN5458 (Regeneron) and PF-06863135 (Pfizer); and other novel agents such as ibrutinib (Abbvie/Roche), venetoclax (Abbvie), plitidepsin (PharMar), masitinib (AB Sciences), filanesib (Array Biopharma), oprozomib (Amgen), ricolinostat (Celgene) and melflufen (Oncopeptides).

***Non-Hodgkin s Lymphoma (NHL)***

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan®, Roche). In patients with DLBCL who are not elderly and who have good organ function, high dose chemotherapy with stem cell transplantation is often used. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica®, Pharmacyclics) and the immunomodulatory drug lenalidomide (Revlimid®, Celgene) have shown activity in DLBCL. There are also a number of other widely used anti-cancer agents that have broad labels which include NHL, and some of these are being evaluated alone or in combination for the treatment of patients with DLBCL that have relapsed after treatment with chemotherapy. Other anti-cancer agents are also being evaluated in the treatment of DLBCL, including but not limited to, MOR-208 (MorphoSys), polatuzumab vedotin (Roche), umbralisib/ublituximab (TG Therapeutics), mosunetuzumab (Roche), ADCT-402 (ADC Therapeutics), zanubrutinib (Beigene), Afinitor® (everolimus, Novartis), venetoclax (Abbvie), acalabrutinib (Acerta Pharma), Blinicyto (blinatumomab, Amgen), Imfinzi (durvalumab, AstraZeneca), Opdivo® (nivolumab, BMS), Bavencio (avelumab, Pfizer/EMD Serono) and Adcetris® (brentuximab vendotin, Seattle Genetics). In addition, Kymriah (Novartis) and Yescarta (Kite/Gilead), both CAR-T therapies, have been approved as a treatment for patients with DLBCL and other CAR-T therapies are currently in clinical development.

***Competition with XPO1 Inhibitors***

Drug compounds currently in preclinical studies, if developed and approved, could also be competitive with our drug candidates, if approved. In January 2015, Stemline Therapeutics, Inc. announced that it had exclusively licensed the rights to develop and commercialize SL-801, an XPO1 inhibitor, from CanBas Co., Ltd. In December 2015, Stemline announced the opening of its IND application and planned initiation of a clinical development program in multiple



cancer types. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors. Additionally, Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb

## **Table of Contents**

Company) has evaluated compounds derived from leptomycin B in preclinical studies. To our knowledge, the Kosan compounds are not currently being developed and have never entered human studies.

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

### ***Competition with PAK4/NAMPT Dual Inhibitors***

Our first-in-class PAK4/NAMPT dual inhibitor KPT-9274, if developed and approved, would compete with currently-marketed therapies and drugs in clinical development to treat cancer. However, there are currently no marketed therapies that selectively target PAK4 and/or NAMPT. Pfizer Inc. developed PF-03758309, a non-selective PAK inhibitor, meaning that this compound inhibited several of the PAK family members, and not solely PAK4, through Phase 1 clinical development, but that compound had poor oral bioavailability in both animals and humans and, to our knowledge, development has been discontinued. We are aware that PAK4 biology is being evaluated preclinically by AstraZeneca plc and Genentech, Inc. (acquired by Roche Holding AG). We are not aware of any PAK4 inhibitors that are in clinical development at the present time.

In addition to KPT-9274, we are aware of three NAMPT inhibitors that have advanced into human clinical trials. These compounds include GMX1778 (also known as CHS-828), GMX1777 (water-soluble derivative of GMX1778), and APO866 (also known as FK866 and WK175). To our knowledge development of these inhibitors were discontinued. We are aware that NAMPT biology is being evaluated by Genentech, Inc., Eli Lilly & Company, Millennium/Takeda Pharmaceutical Company Ltd., OncoTartis, Inc., Aurigene Discovery Technologies Limited, and at some academic institutions. We are not aware of any other NAMPT inhibitors in clinical development.

### **Manufacturing**

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacture of our drug candidates for preclinical and clinical testing, as well as for commercial manufacture if our drug candidates receive marketing approval. In preparation for a potential commercial launch of selinexor in the United States subject to marketing approval by the FDA, we entered into a long-term supply arrangement with a third-party manufacturer to provide commercial tablets of selinexor. We have engaged a third party manufacturer to obtain the active pharmaceutical ingredient for selinexor for preclinical and clinical testing and a separate third-party manufacturer for fill-and-finish services. We obtain our selinexor supplies for preclinical and clinical testing from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place for supplies for preclinical and clinical testing. We do not currently have arrangements in place for redundant supply.

All of our drug candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

### **Government Regulation**

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, or EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling,

## **Table of Contents**

advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

### **Review and Approval of Drugs in the United States**

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

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

submission to the FDA of an IND, which must take effect before human clinical trials may begin;

approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;

performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;

preparation and submission to the FDA of an NDA;

review of the product by an FDA advisory committee, where appropriate or if applicable;

satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;

satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

payment of user fees and securing FDA approval of the NDA; and

compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

***Preclinical Studies***

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive

## **Table of Contents**

adverse events and carcinogenicity, may continue after the IND is submitted. In addition, companies usually must also develop additional information about the chemistry and physical characteristics of the investigational product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the candidate product and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the candidate product does not undergo unacceptable deterioration over its shelf life.

### ***The IND and IRB Processes***

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

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with FDA certain regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or an NDA. The final rule provides that such studies must be conducted in accordance with good clinical practice, or GCP, including review and approval by an independent ethics committee and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must

conduct a continuing review and reapprove the study at least annually. The IRB must review and

## **Table of Contents**

approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee or DSMB. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

### ***Human Clinical Trials in Support of an NDA***

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

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

- Phase 1: The drug is initially introduced into a small number of healthy human subjects or patients with the target disease (e.g. cancer) or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. These clinical trials are commonly referred to as pivotal studies, which denotes a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug.

Phase 4:



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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on

## **Table of Contents**

various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

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

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

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is \$2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2019 of \$309,915. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses.

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

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. The FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain drug applications, including applications for drugs in a shortage or drugs for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the

potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of

## **Table of Contents**

treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

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

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of

such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

## **Table of Contents**

Finally, with passage of the 21st Century Cures Act, or Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy (as defined in the Cures Act) that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

### ***Accelerated Approval Pathway***

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

### ***The FDA's Decision on an NDA***

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may

## **Table of Contents**

require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

### ***Post-Approval Requirements***

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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

restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;



finances, 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.

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**Table of Contents**

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, healthcare professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementation regulations, as well as the Drug Supply Chain Security Act, or DSCSA, which regulates the distribution of and tracing of prescription drugs and prescription drug samples at the federal level, and sets minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCSA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

***Section 505(b)(2) NDAs***

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the Section 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.



## **Table of Contents**

### ***Abbreviated New Drug Applications for Generic Drugs***

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is bioequivalent to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug...

Upon approval of an ANDA, the FDA indicates whether the generic product is therapeutically equivalent to the RLD in its publication Approved Drug Products with Therapeutic Equivalence Evaluations, also referred to as the Orange Book. Clinicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing clinicians or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new legislation also authorizes FDA to expedite review of competitor generic therapies or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

### ***Hatch-Waxman Patent Certification and the 30-Month Stay***

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the

## **Table of Contents**

patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

the required patent information has not been filed;

the listed patent has expired;

the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

### ***Pediatric Studies and Exclusivity***

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time. For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss

## **Table of Contents**

deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with drug sponsors. The legislation requires FDA to meet with drug sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety days after FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which a generic (ANDA or 505(b)(2) NDA) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by a proposed generic product.

### ***Orphan Drug Designation and Exclusivity***

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

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

Orphan drug exclusivity will not bar approval of another orphan drug under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Legislation reverses prior precedent holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of



clinical superiority.

## **Table of Contents**

### ***Patent Term Restoration and Extension***

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA. We cannot provide any assurance that any patent term extension with respect to any U.S. patent will be obtained and, if obtained, the duration of such extension, in connection with any of our product candidates.

### ***The 21st Century Cures Act***

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

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

### ***Review and Approval of Animal Drugs in the United States***

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

To begin this process, an applicant must file an Investigational New Animal Drug application, or INAD, with the CVM. The applicant will hold a pre-development meeting with the CVM to reach general agreement on the plans for providing the data necessary to fulfill requirements for a NADA. In this context, an applicant must

## **Table of Contents**

submit pivotal protocols to the CVM for review and concurrence prior to conducting the required studies. The applicant will gather and submit data on safety, efficacy and chemistry, manufacturing and controls or CMC to the CVM for review, as below:

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

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

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

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

## **Review and Approval of Drug Products in the European Union**

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve

additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

**Table of Contents**

***Procedures Governing Approval of Drug Products in the European Union***

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

To obtain marketing approval of a product under EU regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or EMA, is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various EU member states where such product has not received marketing approval in any EU member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate pre-clinical tests and clinical trials. Such applications are necessary when the proposed product does not meet the strict definition of a generic medicinal product, or bioavailability studies cannot be used to

demonstrate bioequivalence, or there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the

## **Table of Contents**

reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Hybrid medicinal product applications have automatic access to the centralized procedure when the reference product was authorized for marketing via that procedure. Where the reference product was authorized via the decentralized procedure, a hybrid application may be accepted for consideration under the centralized procedure if the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization for the medicinal product is in the interest of patients at the community level.

### ***Clinical Trial Approval in the European Union***

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

In April 2014, the EU passed the new Clinical Trials Regulation, (EU) No 536/2014, which will replace the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the EU, the new EU clinical trials legislation was passed as a regulation that is directly applicable in all EU member states. All clinical trials performed in the EU are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (EU) No 536/2014 becomes applicable. According to the current plans of EMA, the new Clinical Trials Regulation will become applicable in 2019. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

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

### ***Periods of Authorization and Renewals***

Marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization



ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited

## **Table of Contents**

period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

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

In the EU, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

### ***Orphan Drug Designation and Exclusivity***

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

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

### ***Regulatory Requirements after Marketing Authorization***

As in the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States

both before and after grant of the manufacturing and marketing authorizations. The holder of an

## **Table of Contents**

EU marketing authorization for a medicinal product must, for example, comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. The manufacturing process for medicinal products in the EU is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, including compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the EU, the advertising and promotion of approved products are subject to EU Member States' laws governing promotion of medicinal products, interactions with clinicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion, which is prohibited in the EU.

### ***Brexit and the Regulatory Framework in the United Kingdom***

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

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

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

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further,

one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

## **Table of Contents**

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

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

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

## **Healthcare Law and Regulation**

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

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

the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willingly executing,

## **Table of Contents**

or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

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

the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, information related to payments and other transfers of value to clinicians and teaching hospitals and clinician ownership and investment interests; and

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

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to clinicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

## **Healthcare Reform**

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

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

an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;



expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

expanded manufacturer's rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of average manufacturer price, or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

**Table of Contents**

expanded the types of entities eligible for the 340B drug discount program;

established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has not been clearly defined. The ACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

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

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent Congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

These healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price for any approved product and/or the level of reimbursement physicians receive for administering any approved product. Reductions in reimbursement levels may negatively impact the prices or the frequency with which products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation

Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the Senate.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, President Trump signed an executive order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a

## Table of Contents

second executive order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the Trump Administration announced that it will discontinue the payment of cost-sharing reduction, or CSR, payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain.

More recently, with the December 2017 enactment of the Tax Cuts and Jobs Act of 2017, Congress repealed the individual mandate. The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

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

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

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs.



**Table of Contents****Employees**

As of February 15, 2019, we had 332 full-time employees. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

**Executive Officers of the Company**

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

| <b>Name</b>                           | <b>Age</b> | <b>Position</b>   |
|---------------------------------------|------------|---|
| Michael G. Kauffman, M.D., Ph.D.      | 55         | Chief Executive Officer and Director  |
| Sharon Shacham, Ph.D., M.B.A.         | 48         | President and Chief Scientific Officer  |
| Ran Frenkel, RPh.                     | 50         | Chief Development Operations Officer  |
| Christopher B. Primiano, J.D., M.B.A. | 38         | Executive Vice President, Chief Business Officer, General Counsel and Secretary |
| Anand Varadan                         | 52         | Executive Vice President, Chief Commercial Officer                              |
| Michael Mason                         | 44         | Senior Vice President, Chief Financial Officer and Treasurer                    |

*Michael G. Kauffman, M.D., Ph.D.* Dr. Kauffman has served as Karyopharm's Chief Executive Officer since January 2011 and has been one of our directors since 2008. Dr. Kauffman co-founded Karyopharm with Dr. Sharon Shacham in 2008 and served as our President from January 2011 to December 2013 and as Chief Medical Officer from December 2012 to December 2013. Prior to joining Karyopharm, he was Chief Medical Officer of Onyx Pharmaceuticals Inc., a biopharmaceutical company, from November 2009 to December 2010. From November 2008 to November 2009, Dr. Kauffman was Chief Medical Officer of Proteolix Inc., which was acquired by Onyx Pharmaceuticals. At Proteolix, he led the development of Kyprolis® (carfilzomib), a novel proteasome inhibitor approved in refractory myeloma by the Food and Drug Administration in July 2012. Dr. Kauffman was an operating partner at Bessemer Venture Partners from 2006 to 2008, where he led investments in biotechnology companies. From 2006 to 2008, he was President and Chief Executive Officer of Epix Pharmaceuticals, Inc., a biopharmaceutical company that underwent liquidation proceedings through an assignment for the benefit of creditors under Massachusetts law in 2009. Dr. Kauffman was President and Chief Executive Officer of Predix Pharmaceuticals, Inc., a private biopharmaceutical company focused on G protein-coupled receptors (GPCR), from 2002 until its merger into Epix Pharmaceuticals in 2006. In that role, he led the merger of Predix Pharmaceuticals and Epix Pharmaceuticals, oversaw the discovery and development of four new clinical candidates and led collaboration transactions with Amgen and GlaxoSmithKline. From March 2000 to September 2002, Dr. Kauffman was Vice President, Clinical at Millennium Pharmaceuticals, Inc., a biopharmaceutical company, where he led the Velcade® development program. From September 1997 to March 2000, Dr. Kauffman held a number of senior positions at Millennium Predictive Medicine, Inc., a biopharmaceutical company and a subsidiary of Millennium Pharmaceuticals, where he led the discovery and development of novel molecular diagnostics for major cancers, including melanoma, and led transactions with Becton-Dickenson and Bristol Myers Squibb. From August 1995 to September 1997, Dr. Kauffman held a number of senior positions at Biogen Idec, Inc., a biopharmaceutical company, where he led the clinical development of anti-CD40L antibodies in autoimmune and inflammatory diseases, and acted as the main medical advisor to the Biogen business development group. Dr. Kauffman currently serves on the board of directors, nominating and governance committee and research and development committee of Infinity Pharmaceuticals, Inc., a public biopharmaceutical company, on the board of directors and audit committee and as chairman of the

compensation committee of Kezar Life Sciences, Inc., a public biopharmaceutical company, and on the board of directors and compensation committee of Verastem Inc., a public biopharmaceutical company. Dr. Kauffman previously served on the board of directors and compensation and audit committees of Zalicus Inc., a biotechnology company. Dr. Kauffman received his B.A. in Biochemistry from Amherst College and his M.D. and Ph.D. from Johns Hopkins Medical School, and he trained in internal medicine and rheumatology at

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**Table of Contents**

Beth Israel Hospital (now Beth Israel Deaconess Medical Center) and Massachusetts General Hospital. He is board certified in internal medicine.

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

*Michael Mason, C.P.A., M.B.A.* Mr. Mason was appointed Senior Vice President, Chief Financial Officer and Treasurer of the Company on February 25, 2019. Additionally, Mr. Mason has also been designated as the Company's principal financial officer and principal accounting officer, effective on March 2, 2019 following the filing of this Form 10-K. Mr. Mason served as Vice President of Finance and Treasurer of Alynlyam Pharmaceuticals, Inc., a public biopharmaceutical company, from February 2011 until February 2019, as its Principal Accounting Officer from February 2011 to October 2018, and as its Principal Financial Officer from February 2011 to June 2016 and from January 2017 to May 2017. From December 2005 to February 2011, Mr. Mason served as Alynlyam's Corporate Controller. From May 2000 through November 2005, Mr. Mason served in several finance and commercial roles at Praecis Pharmaceuticals Incorporated, a public biotechnology company, most recently as Corporate Controller. Prior to Praecis, Mr. Mason worked in the audit practice at KPMG LLP, a national audit, tax and advisory services firm. Mr. Mason received a B.A. in Business Administration from Stetson University and an M.B.A. from Babson College and is a certified public accountant.

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

*Christopher B. Primiano, J.D., M.B.A.* Mr. Primiano joined Karyopharm in March 2014 as Vice President, Corporate Development, General Counsel and Secretary, and was appointed Senior Vice President, Corporate Development, General Counsel and Secretary in September 2015; Senior Vice President, Operations, Business Development, General Counsel and Secretary in November 2016 and Executive Vice President, Chief Business Officer, General Counsel and Secretary in January 2017. Prior to joining Karyopharm, Mr. Primiano was a Counsel at Wilmer Cutler



Pickering Hale and Dorr LLP, where he had practiced law since October 2012. From August 2010 to August 2012, he served as Vice President, Corporate Development, General Counsel and

## **Table of Contents**

Secretary of GlassHouse Technologies, Inc., an information technology consulting company, where he led global legal operations and managed asset and subsidiary acquisition and sale activity. Mr. Primiano began his career at Gunderson Dettmer Stough Villeneuve Franklin & Hachigian LLP, where he practiced law from August 2006 to July 2010. Mr. Primiano received a B.A. in Political Economy and English from Georgetown University, an M.B.A. from the Boston College Carroll School of Management and a J.D. from Boston College Law School.

*Anand Varadan.* Mr. Varadan has served as Karyopharm's Executive Vice President, Chief Commercial Officer since June 2018. Mr. Varadan has built and led commercial and cross-functional operations and successfully launched and marketed novel therapeutics across a broad array of therapeutic areas. Most recently, Mr. Varadan provided commercial and strategic consultancy services to a variety of biotech companies and investors from September 2016 to June 2016 through his firm, Ignition Insights, LLC. Prior to forming Ignition Insights, he served as Chief Commercial Officer for Chiasma, Inc., a biopharmaceutical company, from August 2015 to June 2016. From January 1999 to July 2015, he served in a progression of commercial leadership and general management roles at Amgen Inc., a biopharmaceutical company, including Vice President, Inflammation and Nephrology Business Unit from April 2014 to July 2015 and Vice President/General Manager, Amgen Canada from September 2011 to April 2014. Prior to Amgen, Mr. Varadan was a brand manager at Procter and Gamble Company. Mr. Varadan received an M.B.A. from the Simon Business School at the University of Rochester and a B.A. in Zoology from The George Washington University.

## **Our Corporate Information**

Karyopharm was incorporated under the laws of the state of Delaware on December 22, 2008 under the name Karyopharm Therapeutics Inc. Our principal executive offices are located at 85 Wells Avenue, 2<sup>nd</sup> Floor, Newton, Massachusetts 02459. Our telephone number is (617) 658-0600, and our website is located at [www.karyopharm.com](http://www.karyopharm.com). References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Form 10-K.

## **Available Information**

Our Internet website is <http://www.karyopharm.com>. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the U.S. Securities and Exchange Commission, or SEC. In addition, we regularly use our website to post information regarding our business, development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors" as a source of information about us.

Our Code of Business Conduct and Ethics, Corporate Governance Guidelines and the charters of the Audit, Compensation and Nominating and Corporate Governance Committees of our board of directors are all available on our website at <http://www.karyopharm.com> at the "Investors" section under "Corporate Governance". Stockholders may request a free copy of any of these documents by writing to Investor Relations, Karyopharm Therapeutics Inc., 85 Wells Avenue, 2<sup>nd</sup> floor, Newton, Massachusetts 02459, U.S.A.

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**Table of Contents**

**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 will depend heavily on the successful development, regulatory approval and eventual commercialization of selinexor. In August 2018, we announced the completion of the rolling submission of a New Drug Application, or NDA, to the U.S. Food and Drug Administration, or FDA, with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the Prescription Drug User Fee Act, or PDUFA. On February 26, 2019, the FDA convened its Oncologic Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol. We cannot predict when or if selinexor will receive marketing approval on accelerated basis, or at all.

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

government payors. If we or our commercialization collaborators are unable to successfully commercialize selinexor, we may not be able to generate sufficient revenues to continue our business.

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**Table of Contents**

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

We currently have no drugs approved for sale and we cannot guarantee that we will ever have marketable drugs. Clinical failure can occur at any stage of clinical development. Clinical trials may produce negative or inconclusive results, and we or any collaborators may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. We will be required to demonstrate with substantial evidence through well-controlled clinical trials that our drug candidates are safe and effective for use in a diverse population before we can seek regulatory approvals for their commercial sale. Success in early-stage clinical trials does not mean that future larger registration clinical trials will be successful because drug candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA and non-U.S. regulatory authorities despite having progressed through early-stage clinical trials. Drug candidates that have shown promising results in early-stage clinical trials may still suffer significant setbacks in subsequent registration clinical trials. Additionally, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later-stage clinical trials, and interim results of a clinical trial are not necessarily indicative of final results. For example, we released top-line results from the expansion of our Selinexor Treatment of Refractory Myeloma (STORM) study in 2018. While we believe the results we observed were positive, the FDA's ODAC reviewed the data in our NDA based on the results from the STORM study and recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. Accordingly, there can be no assurance that results that we believe to be positive will be viewed similarly by regulatory authorities or as sufficient to support a request for registration.

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

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same drug candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. We do not know whether any Phase 2, Phase 3 or other clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain regulatory approval to market our drug candidates.

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

To date, we have had several discussions with the FDA and non-U.S. regulatory authorities regarding the design of our later phase clinical trials for selinexor, including the BOSTON, STORM, SADAL and SEAL studies. We plan to seek regulatory approvals of selinexor in North America and Europe in each indication with

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**Table of Contents**

respect to which such later phase clinical trial is being conducted and with respect to which we receive positive results that may support full or accelerated approval, as the case may be. In August 2018, we announced the completion of the rolling submission of an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the Prescription Drug User Fee Act, or PDUFA. On February 26, 2019, the FDA convened its ODAC to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. We or our current or future partners may also seek such approvals in other geographies. We cannot be certain that we will commence additional later phase trials or complete ongoing later phase trials as anticipated. Before obtaining regulatory approvals for the commercial sale of any drug candidate for a target indication, we must demonstrate with substantial evidence gathered in preclinical studies and well-controlled clinical studies, and, with respect to approval in the United States, to the satisfaction of the FDA, that the drug candidate is safe and effective for use for that target indication. There is no assurance that the FDA or non-U.S. regulatory authorities would consider our current and planned later phase clinical trials to be sufficient to serve as the basis for filing for approval or to gain approval of selinexor for any indication. The FDA and non-U.S. regulatory authorities retain broad discretion in evaluating the results of our clinical trials and in determining whether the results demonstrate that selinexor is safe and effective. If we are required to conduct additional clinical trials of selinexor prior to approval, including additional earlier phase clinical trials that may be required prior to commencing any later phase clinical trials, or additional clinical trials following completion of our current and planned later phase clinical trials, we will need substantial additional funds, and there is no assurance that the results of any such additional clinical trials will be sufficient for approval.

The results to date in preclinical and early clinical studies conducted by us or our academic collaborators and in Phase 1 and Phase 2 clinical trials that we are currently conducting include the response of tumors to selinexor. We expect that in any later phase clinical trial where patients are randomized to receive either selinexor on the one hand, or standard of care, supportive care or placebo on the other hand, the primary endpoint will be either progression free survival, meaning the length of time on treatment until objective tumor progression, or overall survival, while the primary endpoint in any later phase clinical trial that is not similarly randomized may be different. For example, the primary endpoint of our Phase 2/3 SEAL study, the clinical trial of selinexor in patients with dedifferentiated liposarcoma, and a primary endpoint of our Phase 3 BOSTON study, the clinical trial of selinexor in combination with Velcade (bortezomib) and dexamethasone in patients with multiple myeloma, is progression free survival. In some instances, the FDA and other regulatory bodies have accepted overall response rate as a surrogate for a clinical benefit and have granted regulatory approvals based on this or other surrogate endpoints. Overall response rate is defined as the portion of patients with tumor size reduction of a predefined amount for a minimum time period. For some types of cancer, we may use overall response rate as a primary endpoint, as we did in our SADAL study and our STORM study. These clinical trials will not be randomized against control arms and the primary endpoints of these trials are overall response rate. If selinexor does not demonstrate sufficient overall response rates in these indications, or any other indication for which a clinical trial has overall response rate as a primary endpoint, or if the FDA or non-U.S. regulatory authorities do not deem overall response rate a sufficient endpoint, or deem a positive overall response rate to be insufficient, it will likely not be approved for that indication based on the applicable study.

**Table of Contents**

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

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

successful completion of preclinical studies;

acceptance by the FDA of investigational new drug applications, or INDs, for our drug candidates prior to commencing clinical studies;

successful enrollment in, and completion of, clinical trials, including demonstration of a favorable risk-benefit ratio;

receipt of marketing approvals from applicable regulatory authorities;

establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;

obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our drug candidates;

establishing sales, marketing, manufacturing and distribution capabilities to commercialize any drugs for which we may obtain marketing approval, whether alone or in collaboration with others;

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

acceptance of the drugs, if and when approved, by patients, the medical community and third-party payors;

effectively competing with other therapies;

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



maintaining an acceptable safety profile of the drugs following approval;

enforcing and defending intellectual property rights and claims; and

maintaining and growing an organization of scientists and business people, including collaborators, who can develop and commercialize our drug candidates.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our drug candidates, which would materially harm our business.

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

Our SINE compounds inhibit the nuclear export protein XPO1. We believe that no currently approved cancer treatments are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. Despite promising results to date in preclinical studies of selinexor that we have conducted and in Phase 1 and Phase 2 clinical trials of selinexor conducted by us or our academic collaborators, we may not succeed in demonstrating safety and efficacy of SINE compounds in our current and future human

**Table of Contents**

clinical trials. Any drug candidates that we develop may not effectively prevent the exportation of tumor suppressor and/or growth regulatory proteins from the nucleus in humans with a particular form of cancer. If selinexor is unsuccessful in supporting the hypothesis that drug candidates targeting the regulation of intracellular transport of XPO1 have commercial value or experiences significant delays in doing so, our business may be materially harmed and we may not be able to generate sufficient revenues to continue our business.

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

Part of our strategy involves identifying and developing drug candidates to build a pipeline of novel drug candidates. Our drug discovery efforts may not be successful in identifying compounds that are useful in treating cancer or other diseases. Our research programs may initially show promise in identifying potential drug candidates, yet fail to yield drug candidates for clinical development for a number of reasons, including:

the research methodology used may not be successful in identifying potential drug candidates;

potential drug candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and/or achieve market acceptance; or

potential drug candidates may not be effective in treating their targeted diseases.

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

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

***Clinical drug development is a lengthy and expensive process, with an uncertain outcome. If clinical trials of our drug candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our drug candidates.***

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

clinical trial could negatively impact the perception of our other drug candidates and/or cause the FDA or other regulatory authorities to require additional testing before any of our drug candidates are approved.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our drug candidates, including:

regulatory authorities or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

**Table of Contents**

feedback from regulatory authorities that requires us to modify the design of our clinical trials;

we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites or contract research organizations;

clinical trials of our drug candidates may produce negative or inconclusive results, and we may decide, or regulatory authorities may require us, to conduct additional clinical trials, suspend ongoing clinical trials or abandon drug development programs;

the number of patients required for clinical trials of our drug candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

our third-party contractors, including those manufacturing our drug candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

we or our investigators might have to suspend or terminate clinical trials of our drug candidates for various reasons, including non-compliance with regulatory requirements, a finding that our drug candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;

regulators may recommend or require us to perform additional or unanticipated clinical trials to obtain approval;

regulators may revise the requirements for approving our drug candidates, or such requirements may not be as we anticipate;

the cost of clinical trials of our drug candidates may be greater than we anticipate;

the supply or quality of our drug candidates or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate;

regulators may revise the requirements for approving our drug candidates, or such requirements may not be as we anticipate; and

any partners and collaborators that help conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us.

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

be delayed in obtaining marketing approval for our drug candidates;

not obtain marketing approval at all;

obtain marketing approval in some countries and not in others;

obtain approval for indications or patient populations that are not as broad as intended or desired;

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

**Table of Contents**

schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our drug candidates, allow our competitors to bring drugs to market before we do or impair our ability to successfully commercialize our drug candidates, which would harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of regulatory approval of our drug candidates.

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

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

Patient enrollment is affected by other factors, including:

severity of the disease under investigation;

availability and efficacy of approved drugs for the disease under investigation;

patient eligibility criteria for the study in question;

competing drugs in clinical development;

perceived risks and benefits of the drug candidate under study;

restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;

efforts to facilitate timely enrollment in clinical trials;

patient referral practices of physicians;

the ability to monitor patients adequately during and after treatment; and

proximity and availability of clinical trial sites for prospective patients.

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

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

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**Table of Contents**

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

***If serious adverse or unacceptable side effects are identified 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 or it could delay or prevent regulatory approval, limit commercial viability, or result in significant negative consequences following any marketing approval.***

Four of our drug candidates are in clinical development for treatment of human diseases. Their risk of failure is high. It is impossible to predict when or if any of our drug candidates will prove effective or safe in humans or will receive marketing approval. If our drug candidates are associated with undesirable side effects or have characteristics that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. For example, we have modified our informed consent form and advised patients already enrolled in our clinical trials of the potential for worsening of pre-existing cataracts as a result of treatment with selinexor. Adverse events, or AEs, in our clinical trials to date have been generally predictable and manageable, although some patients have experienced more serious AEs. The most common drug-related AEs were gastrointestinal, such as nausea, anorexia, diarrhea and vomiting, and fatigue. These side effects were generally mild or moderate in severity. The most common AEs that were Grade 3 or Grade 4, meaning they were more than mild or moderate in severity, were thrombocytopenia, or low count of platelets in the blood, and neutropenia, or low neutrophil counts. To date, the most common AEs have been managed with supportive care and dose modifications. However, a number of patients have withdrawn from our clinical trials as a result of AEs. For example, in Part 2 of the STORM study each patient experienced at least one AE, approximately 78.0% of patients received a dose modification of selinexor during the study as a result of AEs and approximately 26.8% of patients discontinued use of selinexor during the study as a result of AEs. A small percentage of patients across our clinical trials have experienced SAEs deemed by us and the clinical investigator to be related to selinexor. SAEs generally refer to AEs that result in death, are life threatening, require hospitalization or prolonging of hospitalization, or cause a significant and permanent disruption of normal life functions, congenital anomalies or birth defects, or require intervention to prevent such an outcome.

These AEs and the resulting dose modification and/or treatment discontinuation rates or safety or toxicity issues that we may experience in our clinical trials in the future could result in a more restrictive label for any drug candidates approved for marketing or could result in the delay or denial of approval to market any drug candidates by the FDA or comparable foreign regulatory authorities, which could prevent us from ever generating revenue from the sale of drugs or achieving profitability. Results of our trials could reveal an unacceptably high severity and prevalence of side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our drug candidates for any or all targeted indications. Many compounds that initially showed promise in early-stage trials for treating cancer or other diseases have later been found to cause side effects that prevented further development of the compound. If such an event occurs after any of our drug candidates are approved, a number of potentially significant negative consequences may result, including:

regulatory authorities may withdraw the approval of such drug;



regulatory authorities may require additional warnings on the label or impose distribution or use restrictions;

regulatory authorities may require one or more postmarketing studies;

regulatory authorities may withdraw the approval of such drug;

**Table of Contents**

we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;

we could be sued and held liable for harm caused to patients; and

our reputation may suffer.

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

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

We, and our clinical trial investigators, currently determine if serious adverse or unacceptable side effects are drug-related. The FDA or non-U.S. regulatory authorities may disagree with our or our clinical trial investigators interpretation of data from clinical trials and the conclusion by us or our clinical trial investigators that a serious adverse effect or unacceptable side effect was not drug-related. The FDA or non-U.S. regulatory authorities may require more information, including additional preclinical or clinical data to support approval, which may cause us to incur additional expenses, delay or prevent the approval of one of our drug candidates, and/or delay or cause us to change our commercialization plans, or we may decide to abandon the development or commercialization of the drug candidate altogether.

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

Because we have limited financial and managerial resources, we focus on research programs and drug candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other drug candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and drug candidates for specific indications may not yield any commercially-viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such drug candidate.

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

If any of our drug candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Efforts to educate the medical community and third-party payors on the benefits of our drug candidates will require significant resources and may not be successful. For example, current cancer treatments like chemotherapy and radiation therapy are well-established in the medical community, and doctors may continue to rely on these treatments. If 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;

**Table of Contents**

the ability to offer our drugs for sale at competitive prices;

convenience and ease of administration compared to alternative treatments;

the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

the strength of marketing and distribution support;

the timing of market introduction of competitive products;

sufficient third-party coverage or reimbursement;

effectiveness of our sales and marketing efforts;

adverse publicity about our drugs or favorable publicity about competitive products;

the prevalence and severity of any side effects;

any restrictions on the use of our drugs together with other medications; and

inability of certain types of patients to take our drugs.

Our estimates of the potential market opportunities for our drug candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for selinexor or any other drug candidates may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

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

We are in the process of establishing a sales and marketing infrastructure and our company has not previously sold, marketed or distributed pharmaceutical drugs. To achieve commercial success for any approved drug for which sales and marketing is not the responsibility of any strategic collaborator that we have or may have in the future, we must

either develop a sales, marketing and distribution organization or outsource these functions to other third parties. In the future, we may choose to build a sales, marketing and distribution infrastructure to market or co-promote one or more of our drug candidates, if and when they are approved, or enter into additional collaborations with respect to the sale, marketing and distribution of our drug candidates. We are currently establishing the commercial infrastructure to support a potential launch of selinexor in the United States, and we intend to work with existing and potential partners to establish such commercial infrastructure outside the United States.

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

**Table of Contents**

Factors that may inhibit our efforts to commercialize our drugs on our own include:

our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;

the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future drugs;

the lack of complementary drugs to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive drug lines;

unforeseen costs and expenses associated with creating an independent sales, marketing and distribution organization; and

inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies.

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

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

Our license agreements provide for payments on achievement of development and/or commercialization milestones and for royalties on product sales. However, because none of our drug candidates have been approved for commercial sale, our drug candidates are at early stages of development and drug development entails a high risk of failure, we may never realize any material portion of the milestone revenue provided in our license agreements and we do not expect to receive any royalty revenue for several years, if at all.

***We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do.***

The discovery, development and commercialization of new drugs is highly competitive. We face competition with respect to our current drug candidates and will face competition with respect to any drug candidates that we may seek to discover and develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of major pharmaceutical, specialty pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of drugs for the treatment of cancer and the other disease indications for which we are developing our drug candidates, although we believe that to date, none of these competitive drugs and therapies currently in

development are based on scientific approaches that are the same as our approach. Potential competitors also include academic institutions and governmental agencies and public and private research institutions.

We are initially focused on developing our current drug candidates for the treatment of cancer. There are a variety of available therapies marketed for cancer. In many cases, cancer drugs are administered in combination to enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic drugs. We expect that if our drug candidates are approved, they will be priced at a significant premium over competitive generic drugs. This may make it difficult for us to achieve our business strategy of using our drug candidates in combination with existing therapies or replacing existing therapies with our drug candidates.

## **Table of Contents**

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

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

***Even if we are able to commercialize any drug candidates, the drugs may not receive coverage or may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, all of which would harm our business.***

The legislation and regulations that govern marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or drug licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. In the United States, approval and reimbursement decisions are not linked directly, but there is increasing scrutiny from the Congress and regulatory authorities of the pricing of pharmaceutical products. As a result, we might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay our commercial launch of the drug, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

Significant uncertainty exists as to the coverage and reimbursement status of our product candidates for which we seek regulatory approval. Our ability to commercialize any drugs successfully will depend, in part, on the extent to which reimbursement for these drugs and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Obtaining and maintaining adequate reimbursement for our product candidates, if approved, may be difficult. Moreover, the process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for our products, if they are approved, by third-party payors.

A primary trend in the healthcare industry in the United States and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Third-party payors may also seek, with respect to an approved product, additional clinical evidence that goes beyond



the data required to obtain marketing approval. They may require such evidence to demonstrate clinical benefits and value in specific patient populations or they may call for costly pharmaceutical

## **Table of Contents**

studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies before covering our products. Accordingly, we cannot be sure that reimbursement will be available for any drug that we commercialize and, if reimbursement is available, we cannot be sure as to the level of reimbursement and whether it will be adequate. Coverage and reimbursement may impact the demand for, or the price of, any drug candidate for which we obtain marketing approval. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize any drug candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly-approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable regulatory authorities outside of the United States. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

***Product liability lawsuits against us could divert our resources, 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. For example, we may be sued if any drug we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against claims that our drug candidates or drugs caused injuries, we will incur substantial liabilities or be required to limit commercialization of our drug candidates. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for any drug candidates or drugs that we may develop;

injury to our reputation and significant negative media attention;

withdrawal of clinical trial participants;

initiation of investigations by regulators;

product recalls, withdrawals or labeling, marketing or promotional restrictions;

significant costs to defend the related litigation;

substantial monetary awards to trial participants or patients;

loss of revenue;

reduced resources of our management to pursue our business strategy; and

the inability to commercialize any drugs that we may develop.

## **Table of Contents**

We currently hold clinical trial liability insurance coverage, but that coverage may not be adequate to cover any and all liabilities that we may incur. We would need to increase our insurance coverage when we begin the commercialization of our drug candidates for which we obtain marketing approval. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

### ***The business that we conduct outside the United States may be adversely affected by international risk and uncertainties.***

Although our operations are based in the United States, we conduct business outside the United States and expect to continue to do so in the future. For instance, many of the sites at which our clinical trials are being conducted are located outside the United States. In addition, we plan to seek approvals to sell our products in foreign countries. Any business that we conduct outside the United States will be subject to additional risks that may materially adversely affect our ability to conduct business in international markets, including:

potentially reduced protection for intellectual property rights;

the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;

unexpected changes in tariffs, trade barriers and regulatory requirements;

economic weakness, including inflation, volatility in currency exchange rates or political instability in particular foreign economies and markets;

workforce uncertainty in countries where labor unrest is more common than in the United States;

production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;

business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, hurricanes, typhoons, floods and fires; and

failure to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act, or FCPA.

### **Risks Related to Our Financial Position, Convertible Senior Notes and Need for Additional Capital**

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

Since inception, we have incurred significant operating losses. Our net losses were \$178.4 million, \$129.0 million, and \$109.6 million for the years ended December 31, 2018, December 31, 2017 and December 31, 2016, respectively. As of December 31, 2018 and December 31, 2017, we had an accumulated deficit of \$673.7 million and \$495.3 million, respectively. We have not generated any revenue to date from sales of any drugs and have financed our operations to date principally through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, issuance of convertible debt and cash generated from our business development activities. We have devoted substantially all of our efforts to research and development. Our lead drug candidate, oral selinexor, as well as verdinexor, eltanexor and KPT-9274, are in clinical development. Even if we are able to commercialize one of our drug candidates for the treatment of human disease in the near future, we expect to continue to incur significant expenses and operating losses. The net losses we incur may fluctuate significantly from quarter to quarter.

We anticipate that our expenses will continue to increase substantially as compared to prior periods as we prepare for the potential commercialization of selinexor, including due to the impact of increased headcount, to

**Table of Contents**

support our clinical and commercialization activities, expanded infrastructure and increased insurance premiums. If we obtain marketing approval for selinexor, we expect to incur further increased sales, marketing, distribution and outsourced manufacturing expenses.

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

continue our research and preclinical and clinical development of our drug candidates;

initiate additional clinical trials for our drug candidates;

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

establish a sales, marketing and distribution infrastructure to commercialize any drugs for which we may obtain marketing approval, prior to or upon receiving marketing approval;

maintain, expand and protect our intellectual property portfolio;

manufacture our drug candidates;

hire additional clinical, quality control, scientific, commercial and management personnel;

identify additional drug candidates;

acquire or in-license other drugs and technologies;

add operational, financial and management information systems and personnel, including personnel to support our drug development, any future commercialization efforts and our other operations as a public company; and

increase our product liability insurance coverage as we initiate and expand our commercialization efforts. 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 at commercial scale, marketing, selling and distributing those drugs for which we may obtain marketing approval;

establishing and managing any collaborations for the development, marketing and/or commercialization of our drug candidates;

hiring and building a full commercial organization required for the marketing, selling and distribution for those drugs for which we obtain marketing approval;

achieving an adequate level of market acceptance and obtaining and maintaining coverage and adequate reimbursement from third-party payors for any drugs we commercialize; and

obtaining, maintaining and protecting our intellectual property rights.

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

## **Table of Contents**

We may be unable to develop and commercialize selinexor or any other drug candidate and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business and/or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

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

We were incorporated in 2008 and commenced operations in 2009. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our platform, identifying potential drug candidates and conducting preclinical studies and early-phase and later-phase clinical trials of our drug candidates. Our lead drug candidate is currently in multiple Phase 2 and Phase 3 clinical trials and all of our other drug candidates for the treatment of human disease are in early clinical development. We have not yet demonstrated our ability to successfully complete any late-phase clinical trials in humans, including large-scale clinical trials, obtain marketing approvals, manufacture a commercial scale drug, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful drug commercialization. Typically, it takes about six to ten years to develop one new drug from the time it is in Phase 1 clinical trials to when it is commercially available for treating patients. Consequently, any predictions stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

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

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

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

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical trials of, and seek marketing approval and prepare for commercialization of, selinexor and our other drug candidates. We have begun to incur commercialization expenses related to selinexor, including beginning to build a commercial infrastructure, and expect to incur additional commercialization expenses in advance of potentially receiving marketing approval for selinexor. If we obtain marketing approval for any of our drug candidates, we expect to incur significant additional 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, hiring additional personnel and expanding our facilities. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and drug development programs or commercialization efforts.



We expect that our existing cash, cash equivalents and investments will enable us to fund our current operating and capital expenditure plans for at least twelve months from the date of issuance of the financial

**Table of Contents**

statements contained in this Form 10-K while we are establishing the commercial infrastructure for a potential launch of selinexor in the United States. Our future capital requirements will depend on many factors, including:

the progress and results of our current and planned clinical trials of selinexor;

the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our other drug candidates;

the costs, timing and outcome of regulatory review of our drug candidates, including whether any additional clinical trials or other activities are required for approval or label expansion;

our ability to establish and maintain collaborations on favorable terms;

the success of any collaborations that we have entered into and may enter into with third parties;

the extent to which we acquire or in-license other drugs and technologies;

the costs of commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our drug candidates for which we receive marketing approval, and pre-commercialization costs for our drug candidates incurred prior to receiving, any such marketing approval, including the costs and timing of establishing product sales, marketing, manufacturing and distribution capabilities that are not the responsibility of any collaborator that we may have at such time;

the amount of revenue, if any, received from commercial sales of our drug candidates, should any of our drug candidates receive marketing approval;

the terms and timing of any future collaborations, partnerships, licensing, marketing, distribution or other arrangements that we may establish; and

the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Identifying potential drug candidates, conducting preclinical studies and clinical trials and seeking marketing approvals are time-consuming, expensive and uncertain processes that take years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. Although the FDA has accepted for filing our NDA for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma, we may not receive approval to commercialize selinexor, and even if we do, the resulting revenue is not likely to enable us to achieve profitability in the near term. 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 several months or which could take possibly several years to be commercially available, 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. Adequate additional financing may not be available to us on acceptable terms, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit reduce or development activities for one or more of our drug candidates or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our drug candidates.

***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

**Table of Contents**

additional capital through the sale of equity or convertible debt securities, the ownership interests of stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through further collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our future revenue streams, research programs or drug candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our research and drug development or commercialization efforts or grant rights to develop and market drug candidates that we would otherwise prefer to develop and market ourselves.

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

Global credit and financial markets have experienced extreme disruptions over some of the past several years. Such disruptions have resulted, and could in the future result, in diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that any deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be compromised by economic downturns, a volatile business environment and unpredictable and unstable market conditions. If the equity and credit markets deteriorate, it may make any necessary equity or debt financing more difficult to secure, more costly or more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could harm our growth strategy, financial performance and stock price and could require us to delay or abandon plans with respect to our business, including clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers or other third parties with which we conduct business may not survive difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

***Our indebtedness could limit cash flow available for our operations, expose us to risks that could adversely affect our business, financial condition and results of operations and impair our ability to satisfy our obligations under the Notes.***

We incurred \$172.5 million of indebtedness as a result of the sale of the Notes. We may also incur additional indebtedness to meet future financing needs. Our indebtedness could have significant negative consequences for our security holders and our business, results of operations and financial condition by, among other things:

increasing our vulnerability to adverse economic and industry conditions;

limiting our ability to obtain additional financing;

requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, which will reduce the amount of cash available for other purposes;

limiting our flexibility to plan for, or react to, changes in our business;

diluting the interests of our existing stockholders as a result of issuing shares of our common stock upon conversion of the Notes; and

placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital.

Our business may not generate sufficient funds, and we may otherwise be unable to maintain sufficient cash reserves, to pay amounts due under our indebtedness, including the Notes, and our cash needs may increase in the future.

**Table of Contents**

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

Our ability to pay the principal of or interest and additional interest, if any, on the Notes or to make cash payments in connection with any conversion of the Notes depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service the Notes or other future indebtedness and make necessary capital expenditures. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring indebtedness or obtaining additional debt financing or equity capital on terms that may be onerous or highly dilutive. Our ability to refinance the Notes or other future indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations, including the Notes.

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

Holders may require us to repurchase their Notes following a fundamental change at a cash repurchase price generally equal to the principal amount of the Notes to be repurchased, plus accrued and unpaid interest and additional interest, if any. In addition, upon conversion, unless we elect to deliver solely shares of our common stock to settle conversions (other than paying cash in lieu of delivering any fractional share), we must satisfy the conversion in cash. We may not have enough available cash or be able to obtain financing at the time we are required to repurchase the Notes, pay cash amounts due upon conversion or redemption of the Notes or refinance the Notes. In addition, our ability to repurchase the Notes, to pay cash upon conversion or redemption of the Notes or to refinance the Notes may be limited by law, regulatory authority or agreements governing any future indebtedness that we may incur. Our failure to repurchase notes at a time when the repurchase is required by the indenture governing the Notes or to pay cash upon conversion of the Notes as required by the indenture would constitute a default under the indenture. A default under the indenture or the fundamental change itself could also lead to a default under agreements governing our future indebtedness, if any. Moreover, the occurrence of a fundamental change under the indenture could constitute an event of default under any such agreements. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the Notes or to pay cash upon conversion of the Notes.

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

In the event the conditional conversion feature of the Notes is triggered, holders of Notes will be entitled to convert the Notes at any time during specified periods at their option. If one or more holders elect to convert their Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock (other than paying cash in lieu of delivering any fractional share), we would be required to settle a portion or all of our conversion obligation in cash, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal amount of the Notes as a current rather than long-term liability, which would result in a material reduction of our net working capital.

***The accounting method for convertible debt securities that may be settled in cash, such as the Notes, could have a material effect on our reported financial results.***

In May 2008, the Financial Accounting Standards Board, or FASB, issued FASB Staff Position No. APB 14-1, Accounting for Convertible Debt Instruments That May Be Settled in Cash upon Conversion (Including

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**Table of Contents**

Partial Cash Settlement), which has subsequently been codified as Accounting Standards Codification 470-20, Debt with Conversion and Other Options, or ASC 470-20. Under ASC 470-20, an entity must separately account for the liability and equity components of the convertible debt instruments (such as the Notes) that may be settled entirely or partially in cash upon conversion in a manner that reflects the issuer's economic interest cost. The effect of ASC 470-20 on the accounting for the Notes is that the equity component is required to be included in the additional paid-in capital section of stockholders' equity on our consolidated balance sheet at the issuance date, and the value of the equity component would be treated as debt discount for purposes of accounting for the debt component of the Notes. As a result, we will be required to record a greater amount of non-cash interest expense as a result of the amortization of the discounted carrying value of the Notes to their face amount over the term of the Notes. We will report a larger net loss in our financial results because ASC 470-20 will require interest to include both the amortization of the debt discount and the instrument's coupon interest rate, which could adversely affect our future financial results, the market price of our common stock and the trading price of the Notes.

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

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

**Risks Related to Our Dependence on Third Parties**

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

We intend to maintain our existing collaborations and will continue to seek additional third-party collaborators for certain aspects of the development, marketing and/or commercialization of our drug candidates. For example, we have entered into license arrangements with Ono Pharmaceutical Co., Ltd. and Antengene Therapeutics Limited, and plan to continue to seek to enter into additional license relationships, for marketing and commercialization of selinexor for other geographies outside the United States. In addition, we intend to seek one or more collaborators to aid in the further development, marketing and/or commercialization of our other SINE compounds for indications outside of oncology. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In connection with any such arrangements with third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development, marketing and/or commercialization of our drug candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our drug candidates pose the following risks to us:



collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;

**Table of Contents**

collaborators may not perform their obligations as expected or in compliance with applicable regulatory requirements;

collaborators may not pursue development, marketing and/or commercialization of our drug candidates or may elect not to continue or renew development, marketing or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;

collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a drug candidate, repeat or conduct new clinical trials or require a new formulation of a drug candidate for clinical testing;

collaborators could independently develop, or develop with third parties, drugs that compete directly or indirectly with our drugs or drug candidates if the collaborators believe that competitive drugs are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

a collaborator with marketing and distribution rights to one or more drugs may not commit sufficient resources to the marketing and distribution of such drug or drugs;

disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of drug candidates, might lead to additional responsibilities for us with respect to drug candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

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

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

we may lose certain valuable rights under circumstances identified in any collaboration arrangement that we enter into, such as if we undergo a change of control;

collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development, marketing and/or commercialization of the applicable drug candidates;

collaborators may learn about our discoveries and use this knowledge to compete with us in the future; and

the number and type of our collaborations could adversely affect our attractiveness to collaborators or acquirers.

Collaboration agreements may not lead to development or commercialization of drug candidates in the most efficient manner, or at all. If our collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of our collaborators.

## **Table of Contents**

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

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

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside of the United States, the potential market for the subject drug candidate, the costs and complexities of manufacturing and delivering such drug candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of intellectual property, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative drug candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our drug candidate.

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

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

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

***We rely on some third parties as we conduct our clinical trials and some aspects of our research and preclinical studies, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.***

We rely on some third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, as we conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical studies. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our drug development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that 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

## **Table of Contents**

credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The European Medicines Agency, or EMA, also requires us to comply with comparable standards. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our drug candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our drug candidates. In such an event, our financial results and the commercial prospects for our drug candidates could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of such third parties could delay clinical development or marketing approval of our drug candidates or commercialization of our drugs, producing additional losses and depriving us of potential revenue from sales of drugs.

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

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

Such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from the investigator-sponsored trials. However, we do not have control over the timing and reporting of the data from investigator-sponsored trials, nor do we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of our drug candidates. Further, if investigators or institutions breach their obligations with respect to the clinical development of our drug candidates, or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or non-U.S. regulatory authorities may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or non-U.S. regulatory authorities may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may initiate our planned trials and/or may not accept such additional data as adequate to initiate our planned trials.



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**Table of Contents**

*We contract with third parties for the manufacture of our drug candidates for preclinical studies and clinical trials and expect to continue to do so for clinical trials and ultimately for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.*

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our drug candidates for preclinical studies and clinical trials under the guidance of members of our organization. We have engaged third-party manufacturers for drug substance and drug product services. We do not have a long term supply agreement with any of these third-party manufacturers, and we purchase our required drug supplies on a purchase order basis.

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

reliance on the third party for regulatory compliance and quality assurance;

the possible breach of the manufacturing agreement by the third party;

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

equipment malfunctions, power outages or other general disruptions experienced by our third-party manufacturers to their respective operations and other general problems with a multi-step manufacturing process;

the possible misappropriation or disclosure by the third party or others of our proprietary information, including our trade secrets and know-how; and

the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

If any of our drug candidates are approved by any regulatory agency, we intend to enter into agreements with third-party contract manufacturers for the commercial production of those products. This process is difficult and time consuming and we may face competition for access to manufacturing facilities, as there are a limited number of contract manufacturers operating under current Good Manufacturing Practices, or cGMPs, that are capable of manufacturing our drug candidates. Consequently, we may not be able to reach agreement with third-party



manufacturers on satisfactory terms, which could delay our commercialization.

Third-party manufacturers may not be able to comply with current Good Manufacturing Practices, or cGMP, regulations or similar regulatory requirements outside of the United States. Facilities used by our third-party manufacturers must be inspected by the FDA after we submit an NDA and before potential approval of the drug candidate. Similar regulations apply to manufacturers of our drug candidates for use or sale in foreign countries. We do not control the manufacturing process and are completely dependent on our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our drug candidates. If our manufacturers cannot successfully manufacture material that conforms to the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure the applicable approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture, we may need to find alternative manufacturing facilities, which could result in delays in obtaining approval for the applicable drug candidate as alternative qualified manufacturing facilities may not be available

## **Table of Contents**

on a timely basis or at all. In addition, our manufacturers are subject to ongoing periodic unannounced inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements. Failure by any of our manufacturers to comply with applicable cGMPs or other regulatory requirements could result in sanctions being imposed on us or the contract manufacturer, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply and criminal prosecutions, any of which could significantly and adversely affect supplies of our drug candidates and have a material adverse impact on our business, financial condition and results of operations. Any drugs that we may develop may compete with other drug candidates and drugs for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. If our current contract manufacturers cannot perform as agreed, we may be required to replace those manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our drug candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

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

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

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of drugs are subject to extensive regulation by the FDA and comparable foreign regulatory authorities, whose laws and regulations may differ from country to country. We are not permitted to market our drug candidates in the United States or in other countries until we or any of our collaborators receive approval of an NDA from the FDA or marketing approval from applicable regulatory authorities outside of the United States. Our drug candidates are in early stages of development and are subject to the risks of failure inherent in drug development. In August 2018, we announced the completion of the rolling submission of an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA, granted our request for priority review and assigned an action date of April 6, 2019 under the PDUFA. We also announced the submission of a Marketing Authorization Application to the EMA in January 2019 with a request for conditional approval. On February 26, 2019, the FDA convened its Oncology Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. We have not submitted any other application for, or received any marketing approval of, any of our drug candidates in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain

marketing approvals, including FDA approval of an NDA.

## **Table of Contents**

The process of obtaining marketing approvals, both in the United States and abroad, is a lengthy, expensive and uncertain process. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the drug candidates involved.

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

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

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

In order to market and sell our drugs in the European Union and many other jurisdictions, we and our current or future collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, it is required that the drug be approved for reimbursement before the drug can be approved for sale in that country. We and our collaborators may not obtain approvals from regulatory authorities outside of the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in other countries. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

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



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**Table of Contents**

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

Under the Federal Food, Drug and Cosmetic Act, or FDCA, and implementing regulations, the FDA may grant accelerated approval to a product candidate to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies, upon a determination that the product has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective.

Prior to seeking such accelerated approval, we will continue to seek feedback from the FDA and otherwise evaluate our ability to seek and receive such accelerated approval. We are using the data from our expanded STORM study in penta-refractory multiple myeloma to support a request that the FDA consider granting accelerated approval for selinexor. In August 2018, we announced the completion of the rolling submission of an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review and assigned an action date of April 6, 2019 under the PDUFA. However, the FDA has reiterated to us in its feedback that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments at the time of consideration of the application for accelerated approval. Any approved therapies showing activity in patients with penta-refractory multiple myeloma that may exist at the time the FDA acts on any request we may make for accelerated approval could cause the FDA to deny our request. In addition, the FDA has indicated that additional therapies may receive full approval in multiple myeloma prior to the FDA taking action on our accelerated approval submission, which could mean that, at the time the FDA takes action on our accelerated approval submission, treatment of the penta-refractory group is no longer considered an unmet medical need or a patient population that has exhausted available therapies. The FDA has recommended that we plan for regular approval based on a randomized trial for the evaluation of safety and efficacy of selinexor for the treatment of multiple myeloma, and has previously indicated to us its preference for studies that isolate the effects of individual drugs. On February 26, 2019, the FDA convened its Oncologic Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. If the FDA does not grant marketing approval based on our NDA requesting accelerated approval, we will need to wait until the results of the randomized Phase 3 BOSTON study are available to seek regular approval of selinexor as a treatment for relapsed/refractory multiple myeloma, assuming those results are positive, and

there can be no assurance that the FDA will grant such approval.

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**Table of Contents**

Similarly, we intend to use the data from the SADAL study to support an NDA request that the FDA consider granting accelerated approval for selinexor in relapsed and/or refractory diffuse large B-cell lymphoma, or DLBCL and work with the FDA to determine the appropriate timeline for the submission of the NDA. In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. While the FDA has agreed that the current trial design and indication appear appropriate for accelerated approval, they reiterated to us in their feedback that the availability of accelerated approval will depend on the trial results and available therapies at the time of regulatory action. Although we believe that our SADAL study presents an opportunity for us to request that the FDA grant accelerated approval for selinexor in relapsed and/or refractory DLBCL, there can be no assurance that the FDA will grant such approval, whether on an accelerated basis, or at all.

There can also be no assurance that the FDA will agree with our surrogate endpoints or intermediate clinical endpoints, or that we will decide to pursue or submit any additional NDAs for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that, after feedback from FDA, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, for any submission of an application for accelerated approval or application under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted for filing or that any expedited development, review or approval will be granted on a timely basis, or at all.

Moreover, for drugs granted accelerated approval, the FDA typically requires post-marketing confirmatory trials to evaluate the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence. The FDA may withdraw approval of a product candidate approved under the accelerated approval pathway if, for example, the trial required to verify the predicted clinical benefit of our product candidate fails to verify such benefit or does not demonstrate sufficient clinical benefit to justify the risks associated with the drug. The FDA may also withdraw approval if other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use, we fail to conduct any required post approval trial of our product candidate with due diligence or we disseminate false or misleading promotional materials relating to our product candidate. Similar risks to those described above are also applicable to any application that we have submitted or may submit to the EMA to support conditional approval of selinexor to treat penta-refractory multiple myeloma, relapsed/refractory diffuse large B-cell lymphoma, or any other cancer indication. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidates, or withdrawal of a product candidate, would result in a longer time period until commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

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

We may be eligible for fast track designation or breakthrough therapy status for product candidates that we develop. If a product is intended for the treatment of a serious or life-threatening disease or condition and the product demonstrates the potential to address unmet medical needs for this disease or condition, the product sponsor may apply for FDA fast track designation. Additionally, a product candidate may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA has broad discretion



whether or not to grant these designations, so even if we believe a particular product candidate is eligible for such designation or status, the FDA could decide not to grant it. Moreover, even if we do receive such a designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures and there is no assurance that our product candidate will be approved by the FDA.

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**Table of Contents**

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

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

If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the FDA's goal to review an application is six months, rather than the standard review period of ten months. In August 2018, we announced the completion of the rolling submission of an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and granted our request for priority review and assigned an action date of April 6, 2019 under the PDUFA. In addition, we may request priority review in the future for our product candidates in other indications. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. For example, despite the FDA granting our request for priority review of our NDA, during the ODAC meeting to review our NDA, the FDA raised significant issues of concern with the NDA and the ODAC made a non-binding recommendation by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or thereafter.

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

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same product for that time period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is

unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

## **Table of Contents**

Even if we obtain orphan drug exclusivity from the FDA for a product, as we have for selinexor in acute myeloid leukemia, DLBCL and multiple myeloma, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

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

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

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

In addition, manufacturers of approved drugs and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, our collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we or our current or future collaborators receive marketing approval for one or more of our drug candidates, we, and our collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

If we and our collaborators are not able to comply with post-approval regulatory requirements, we and our collaborators could have the marketing approvals for our drugs withdrawn by regulatory authorities, and our or our collaborators' ability to market any future drugs could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

***Any of our drug candidates for which we or our collaborators obtain marketing approval in the future could be subject to post-marketing restrictions or withdrawal from the market, and we and our collaborators may be subject***

***to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our drugs following approval.***

Any of our drug candidates for which we or our collaborators obtain marketing approval in the future, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional

**Table of Contents**

activities for such drug, among other things, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a drug candidate is granted, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a Risk Evaluation and Mitigation Strategy, which could include requirements for a restricted distribution system.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a drug. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we or our collaborators do not market any of our drug candidates for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown AEs or other problems with our drugs or their manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

litigation involving patients taking our drug;

restrictions on such drugs, manufacturers or manufacturing processes;

restrictions on the labeling or marketing of a drug;

restrictions on drug distribution or use;

requirements to conduct post-marketing studies or clinical trials;

warning letters or untitled letters;

withdrawal of the drugs from the market;

refusal to approve pending applications or supplements to approved applications that we submit;

recall of drugs;

finer, restitution or disgorgement of profits or revenues;

suspension or withdrawal of marketing approvals;

damage to relationships with any potential collaborators;

unfavorable press coverage and damage to our reputation;

refusal to permit the import or export of drugs;

drug seizure; or

injunctive or the imposition of civil or criminal penalties.

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

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate

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**Table of Contents**

implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

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

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

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any drugs for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved drugs.

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



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

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;

**Table of Contents**

expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;

a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% starting January 1, 2019) point-of-sale discounts off negotiated prices to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;

extension of manufacturers' Medicaid rebate liability;

expansion of eligibility criteria for Medicaid programs;

expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

new requirements to report certain financial arrangements with physicians and teaching hospitals;

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in April 2013 and, due to subsequent legislative amendments, will stay in effect through 2027 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government

programs may result in a similar reduction in payments from private payors.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with the December 2017 enactment of the Tax Cuts and Jobs Act of 2017, Congress repealed the individual mandate. The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called Cadillac tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the

## **Table of Contents**

medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the donut hole. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

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

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop commercialize product candidates.

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

In addition, on May 11, 2018, the Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the

gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing

**Table of Contents**

information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include gag rules that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

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

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

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any drugs for which we obtain marketing approval. Our future arrangements with third party payors, healthcare providers and physicians may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any drugs for which we obtain marketing approval. These include the following:

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

**False Claims Act** the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including

mandatory treble damages and significant per-claim penalties, currently set at \$5,500 to \$11,000 per false claim;

**HIPAA** the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making

## Table of Contents

false statements relating to healthcare matters, and, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information;

**Transparency Requirements** federal laws require applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and

**Analogous State and Foreign Laws** analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to sales or marketing arrangements and claims involving healthcare items or services and are generally broad and are enforced by many different federal and state agencies as well as through private actions.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of drugs from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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

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

The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, of individuals in the European Union is governed by the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018. It imposes numerous requirements on companies that process personal data,



including requirements relating to: processing health and other sensitive data; obtaining consent of individuals; providing notice to individuals regarding data processing activities; responding to data subject requests; taking certain measures when engaging third-party processors; notifying data subjects and regulators of data breaches; and implementing safeguards to protect the security and confidentiality of personal data. The GDPR imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States. Failure to comply with the requirements of the GDPR may result in fines of up to 20 million Euros

## **Table of Contents**

or four percent of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages. The GDPR increases our responsibility and potential liability in relation to personal data that we process, and we may be required to change our business practices or put in place additional mechanisms ensuring compliance with the GDPR. This may be onerous and adversely affect our business, financial condition, results of operations, and prospects, and despite our efforts, there is a risk that we may be subject to fines, litigation, and reputational harm in connection with our European activities.

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

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

***If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business.***

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.



## **Table of Contents**

***Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain drug candidates outside of the United States and require us to develop and implement costly compliance programs.***

We are subject to numerous laws and regulations in each jurisdiction outside the United States in which we operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

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

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

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the United States, has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and drug candidates outside of the United States, which could limit our growth potential and increase our development costs. The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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

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



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**Table of Contents**

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

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

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

**Risks Related to Our Intellectual Property**

***If we are unable to obtain and maintain patent protection for our drug candidates and other discoveries, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs and other discoveries similar or identical to ours, and our ability to successfully commercialize our drug candidates and other discoveries may be adversely affected.***

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary drug candidates and other discoveries. We seek to protect our 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, 54 patents have issued that relate to XPO1 inhibitors, including composition of matter patents for selinexor, verdinexor and eltanexor in the United States, and their use in targeted therapeutics. In addition, six patents have issued that relate to our PAK4/NAMPT inhibitor, KPT-9274, including a composition of matter patent in the United States and its use in targeted therapeutics. We cannot be certain that any other patents will issue with claims that cover any of our key drug candidates or other discoveries or drug candidates.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our drug candidates or other discoveries, or which effectively prevent others from commercializing competitive drugs and discoveries. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, in some foreign jurisdictions, our ability to secure patents based on our filings in the United States

## Table of Contents

may depend, in part, on our ability to timely obtain assignment of rights to the invention from the employees and consultants who invented the technology. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Assuming the other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside of the United States, the first to file a patent application is entitled to the patent. In March 2013, the United States transitioned to a first-inventor-to-file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application is entitled to the patent. We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, revocation, reexamination, or post-grant or *inter partes* review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our discoveries or drugs and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative discoveries or drugs in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical discoveries and drugs, or limit the duration of the patent protection of our discoveries and drug candidates. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

***We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time-consuming and unsuccessful.***

Competitors or commercial supply companies or others may infringe our patents and other intellectual property rights. For example, we are aware of third parties selling a version of our lead product candidate for research purposes, which may infringe our intellectual property rights. To counter such infringement, we may advise such companies of our intellectual property rights, including, in some cases, intellectual property rights that provide protection for our lead product candidates, and demand that they stop infringing those rights. Such demand may provide such companies the opportunity to challenge the validity of certain of our intellectual property rights, or the opportunity to seek a finding that their activities do not infringe our intellectual property rights. We may also be required to file infringement actions, which can be expensive and time-consuming. In an infringement proceeding, a defendant may assert and a court may agree with a defendant that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the intellectual property at issue. An adverse result in any litigation could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.





## **Table of Contents**

***Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.***

Our commercial success depends upon our ability and the ability of any current and future collaborators to develop, manufacture, market and sell our drug candidates and use our proprietary technologies without infringing the proprietary rights of third parties. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our drug candidates and technology, including interference proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. No litigation asserting such infringement claims is currently pending against us, and we have not been found by a court of competent jurisdiction to have infringed a third party's intellectual property rights. If we are found to infringe or think there is a risk we may be found to infringe, a third party's intellectual property rights, we could be required or choose to obtain a license from such third party to continue developing and marketing our drug candidates and using our technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same intellectual property licensed to us. We could be forced, including by court order, to cease commercializing the infringing intellectual property or drug or to cease using the infringing technology. In addition, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our drug candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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

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

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

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



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**Table of Contents**

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

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

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

Depending upon the timing, duration and conditions of FDA marketing approval, if any, of our drug candidates, one or more of our U.S. patents may be eligible for patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent term extension of up to five years for one patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. The total patent term, including the extension period, may not exceed 14 years following FDA approval. Accordingly, the length of the extension, or the ability to even obtain an extension, depends on many factors.

In the United States, only a single patent can be extended for each qualifying FDA approval, and any patent can be extended only once and only for a single product. Laws governing analogous patent term extensions in foreign jurisdictions vary widely, as do laws governing the ability to obtain multiple patents from a single patent family. Because both selinexor and verdinexor are protected by a single family of patents and applications, we may not be able to secure patent term extensions for both of these drug candidates in all jurisdictions where these drug candidates are approved, if ever.

If we are unable to obtain a patent term extension for a drug candidate or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that drug candidate, if any, in that jurisdiction will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue could be materially reduced.

***If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.***

In addition to seeking patents for our drug candidates and other discoveries, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, contract research organizations, contract

manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information,

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**Table of Contents**

including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. To the extent that we are unable to timely enter into confidentiality and invention or patent assignment agreements with our employees and consultants, our ability to protect our business through trade secrets and patents may be harmed. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed. To the extent inventions are made by a third party under an agreement that does not grant us an assignment of their rights in inventions, we may choose or be required to obtain a license.

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

As of February 1, 2019, four of our trademarks are registered in the United States. We also have eight pending intent-to-use applications in the United States, six of which has been allowed, meaning that we can perfect our registration when we have commenced use in commerce. Outside the United States, we have registrations in the European Union for seven trademarks (potential drug names for selinexor). Applications for the same six trademarks were filed in 15 other jurisdictions, some of which have also proceeded to registration. Applications for two of those marks (XPOVIO and NEXPOVIO) have been filed in an additional twelve jurisdictions. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would, which could adversely affect our business. During trademark registration proceedings in the United States and foreign jurisdictions, we may receive rejections. We are given an opportunity to respond to those rejections, but we may not be able to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings.

In addition, any proprietary name we propose to use with our key drug candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed drug names, including an evaluation of potential for confusion with other drug names. If the FDA objects to any of our proposed proprietary drug names for any of our drug candidates, if approved, we may be required to expend significant additional resources in an effort to identify a suitable proprietary drug name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

**Risks Related to Employee Matters and Managing Growth**

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

We are highly dependent on Michael Kauffman, M.D., Ph.D., our Chief Executive Officer, and Sharon Shacham, Ph.D., M.B.A., our President and Chief Scientific Officer, as well as the other principal members of our management and scientific teams. Although we have entered into formal employment agreements with Drs. Kauffman and Shacham, these agreements do not prevent them from terminating their employment with us at any time. We do not maintain key person insurance for any of our executives or other employees. The loss of the services of any of our key employees could impede the achievement of our research, development, commercialization and other business objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given

**Table of Contents**

the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

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

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

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

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

***Our business and operations may be materially adversely affected in the event of computer system failures or security breaches, and the costs and consequences of implementing data protection measures could be significant.***

Despite the implementation of security measures, our internal computer systems, and those of our contract research organizations and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber attacks, natural disasters, fire, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our reputation or competitive position could be damaged, and the further development and commercialization of our drug candidates could be delayed or halted. We may also be vulnerable to cyber attacks by hackers, or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and adversely affect our business or result in legal proceedings. In addition, the cost and operational consequences of implementing further data protection measures could be significant. Moreover, because the techniques used to obtain unauthorized access, disable or degrade service or sabotage systems change



frequently and often are not

## **Table of Contents**

recognized until launched against a target, we may be unable to anticipate these techniques or to implement adequate security measures.

### **Risks Related to Our Common Stock**

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

As of December 31, 2018, our executive officers, directors and a small number of stockholders own more than a majority of our outstanding common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

*Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.*

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

establish a classified board of directors such that not all members of the board are elected at one time;

allow the authorized number of our directors to be changed only by resolution of our board of directors;

limit the manner in which stockholders can remove directors from the board;

establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

limit who may call stockholder meetings;

authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

**Table of Contents**

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

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

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

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. There can be no assurance that analysts will provide favorable coverage or continue to cover us. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

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

Our stock price has been and is likely to be volatile and may fluctuate substantially. For example, since January 1, 2015, our common stock has traded at prices per share as high as \$38.47 and as low as \$4.26. On February 22, 2019, the closing sale price of our common stock on The Nasdaq Global Select Market was \$5.07 per share. The stock market in general and the market for pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

the success of competitive drugs or technologies;

results of clinical trials of our drug candidates or those of our competitors;

our success in commercializing our drug candidates, if and when approved;

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

## **Table of Contents**

experienced significant stock price volatility in recent years. We may also face securities class action litigation if we cannot obtain regulatory approvals for, or if we otherwise fail to commercialize, selinexor or other of our drug candidates. If we face such litigation, it could result in substantial costs and a diversion of management's attention and our resources, which could harm our business.

### ***We have broad discretion in the use of our cash and cash equivalents and may not use them effectively.***

Our management has broad discretion to use our cash and cash equivalents to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our drug candidates. Pending their use to fund our operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

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

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

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

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

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

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

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares,

**Table of Contents**

could reduce the market price of our common stock. We had 60,829,308 shares outstanding as of December 31, 2018. Of such shares, at least 11.2 million shares are eligible for sale in the public market under Rule 144 of the Securities Act of 1933, as amended, or the Securities Act, subject to the volume limitations and other conditions of Rule 144. The holders of these shares may at any time decide to sell their shares in the public market. We have also registered all shares of common stock that we may issue under our equity compensation plans. As a result, these shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates, to the extent applicable.

***Our ability to use our net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations.***

Under the provisions of the Internal Revenue Code of 1986, as amended, or the Code, our net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (and state tax authorities under relevant state tax rules). In addition, as a result of the Tax Cuts and Jobs Act of 2017, or Tax Act, for U.S. federal income tax purposes, the use of net operating loss carryforwards arising in taxable years beginning after December 31, 2017 is limited to 80% of our taxable income in any future taxable year, although such losses may be carried forward indefinitely. It is uncertain how various states will respond to the Tax Act. Furthermore, the use of net operating loss and tax credit carryforwards may become subject to an annual limitation under Sections 382 and 383 of the Code, respectively, and similar state provisions in the event of certain cumulative changes in the ownership interest of significant shareholders in excess of 50 percent over a three-year period. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of a company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. Our company has completed several financings since its inception which resulted in an ownership change under Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, some of which are outside of our control, could result in ownership changes in the future. For these reasons, we may not be able to use some or all of our net operating loss and tax credit carryforwards, even if we attain profitability.

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

The Tax Act significantly revises the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 34% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely), one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the Tax Act.

**Item 1B. Unresolved Staff Comments**

None.



**Item 2. Properties**

Our headquarters are located in Newton, Massachusetts, where we lease 98,502 square feet of office and laboratory space. We also lease approximately 3,681 square feet of office space in Munich, Germany and 2,153 square feet of office space in Tel Aviv-Yafo, Israel.

**Table of Contents**

**Item 3. Legal Proceedings**

We are not a party to any material legal proceedings.

**Item 4. Mine Safety Disclosures**

Not applicable.

**Table of Contents**

**PART II**

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

**Market Information**

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

**Holders**

As of February 15, 2019, there were nine holders of record of our common stock.

**Dividends**

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

**Table of Contents****Stock Performance Graph**

The following graph shows a comparison from December 31, 2013 through December 31, 2018, of the cumulative total return on an assumed investment of \$100.00 in cash in our common stock as compared to the same investment in the NASDAQ Composite Index and the NASDAQ Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance. Data for the NASDAQ Composite Index and NASDAQ Biotechnology Index assume reinvestment of dividends.

**Cumulative Total Return Comparison**

|                                     | 12/31/13      | 12/31/14      | 12/31/15      | 12/31/16      | 12/31/17      | 12/31/18      |
|-------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| <b>Karyopharm Therapeutics Inc.</b> | <b>100.00</b> | <b>163.31</b> | <b>57.81</b>  | <b>41.01</b>  | <b>41.88</b>  | <b>40.88</b>  |
| <b>NASDAQ Composite</b>             | <b>100.00</b> | <b>114.62</b> | <b>122.81</b> | <b>133.19</b> | <b>172.11</b> | <b>165.84</b> |
| <b>NASDAQ Biotechnology</b>         | <b>100.00</b> | <b>131.71</b> | <b>140.56</b> | <b>112.25</b> | <b>133.67</b> | <b>121.24</b> |

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

**Recent Sales of Unregistered Securities**

None.

**Table of Contents****Item 6. Selected Financial Data**

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

|   | <b>Years Ended December 31,</b>                           |              |              |              |             |
|---|---|--------------|--------------|--------------|-------------|
|   | <b>2018</b>   | <b>2017</b>  | <b>2016</b>  | <b>2015</b>  | <b>2014</b> |
|   | <b>(In thousands, except share and per share amounts)</b> |              |              |              |             |
| <b>Consolidated Statement of Operations Data:</b>                                       |   |              |              |              |             |
| License and other revenue   | \$ 30,336   | \$ 1,605     | \$ 154       | \$ 250       | \$ 229      |
| Operating expenses:   |   |              |              |              |             |
| Research and development  | 161,372   | 107,273      | 86,938       | 97,744       | 60,127      |
| General and administrative  | 48,847  | 24,870       | 23,948       | 21,582       | 15,948      |
| Total operating expenses  | 210,219   | 132,143      | 110,886      | 119,326      | 76,075      |
| Loss from operations  | (179,883)   | (130,538)    | (110,732)    | (119,076)    | (75,846)    |
| Other income, net   | 1,502   | 1,617        | 1,294        | 895          | 69          |
| Loss before income taxes  | (178,381)   | (128,921)    | (109,438)    | (118,181)    | (75,777)    |
| Provision for income taxes  | (26)  | (63)         | (139)        |              |             |
| Net loss  | \$ (178,407)  | \$ (128,984) | \$ (109,577) | \$ (118,181) | \$ (75,777) |
| Net loss per share - basic and diluted  | \$ (3.14)   | \$ (2.81)    | \$ (2.92)    | \$ (3.32)    | \$ (2.43)   |
| Weighted-average number of common shares used in net loss per share - basic and diluted | 56,799,699  | 45,899,784   | 37,523,051   | 35,619,506   | 31,135,694  |

|   | <b>As of December 31,</b> |             |             |             |             |
|---|---------------------------|-------------|-------------|-------------|-------------|
|   | <b>2018</b>               | <b>2017</b> | <b>2016</b> | <b>2015</b> | <b>2014</b> |
|   | <b>(in thousands)</b>     |             |             |             |             |
| <b>Consolidated Balance Sheet Data:</b>           |                           |             |             |             |             |
| Cash, cash equivalents and short-term investments | \$ 328,199                | \$ 146,469  | \$ 129,552  | \$ 175,633  | \$ 205,724  |
| Working capital                                   | 287,708                   | 98,956      | 115,160     | 162,468     | 195,450     |
| Total assets                                      | 341,192                   | 180,294     | 180,385     | 215,443     | 220,337     |
| Convertible senior notes                          | 102,664                   |             |             |             |             |
| Total stockholders' equity                        | 183,170                   | 129,464     | 162,243     | 198,365     | 206,794     |

**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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**Table of Contents****Business Overview****Overview**

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

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. Oral selinexor is being evaluated in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Clinical trials evaluating selinexor include the Phase 2b STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2b SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), the pivotal, randomized Phase 3 BOSTON (**B**ortezomib, **S**elinexor and **D**examethasone) study in multiple myeloma, and the Phase 2/3 SEAL (**S**elinexor in **A**dvanced **L**iposarcoma) study in liposarcoma. During 2018, we reported positive top-line data from the STORM and SADAL studies as well as updated interim data for the STOMP and SEAL studies. As a result of the positive top-line results from the STORM and SADAL studies, we are pursuing or plan to pursue marketing approvals for selinexor in the United States and Europe.

Following the positive outcome from the expanded cohort for the STORM study, in August 2018, we announced the completion of the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. Patients with penta-refractory multiple myeloma have previously received the two proteasome inhibitors (PIs), Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two immunomodulatory drugs (IMiDs), Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI and at least one IMiD, Darzalex®; and their disease has progressed following their most recent therapy. The FDA previously granted orphan drug designation and fast track designation to selinexor for the treatment of patients with penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the Prescription Drug User Fee Act (PDUFA).

We also announced the submission of a Marketing Authorization Application to the European Medicines Agency (EMA) in January 2019 with a request for conditional approval. The EMA's Committee for Medicinal Products for Human Use (CHMP) has granted accelerated assessment for the selinexor Marketing Authorization Application. An accelerated assessment is granted to products deemed by the CHMP to be of major interest for public health and represent therapeutic innovation. Accelerated assessments may reduce the active review time of an MAA from the standard 210 days down to 150 days once it has been validated by the EMA.

On February 26, 2019, the FDA convened its Oncologic Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. The proposed indication discussed at the ODAC meeting was for selinexor in combination with dexamethasone for the



## Table of Contents

treatment of patients with refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

Provided that marketing approval is granted by the FDA, we plan to commercialize selinexor in the United States as a treatment of patients in the approved indication as early as the first half of 2019. We are completing the development of our U.S. commercial capabilities to support a potential launch of selinexor in the United States and recently hired our U.S. sales force and expanded our marketing and market access teams. We will either work with existing and potential partners to establish a commercial infrastructure outside the United States or may, in certain geographies, elect to establish the commercial infrastructure ourselves.

Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients with relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with stem cell rescue), including chimeric antigen receptor modified T (CAR-T) cell therapy and intend to work with the FDA to determine the appropriate timeline for the submission. In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

As of December 31, 2018, we had an accumulated deficit of \$673.7 million. We had net losses of \$178.4 million, \$129.0 million and \$109.6 million for the years ended December 31, 2018, 2017 and 2016, respectively. To date, we have not generated revenues from drug sales. We have financed our operations to date principally through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, issuance of convertible debt and cash generated from our business development activities.

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

continue our research and preclinical and clinical development of our drug candidates;

initiate additional clinical trials for our drug candidates;

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

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

maintain, expand and protect our intellectual property portfolio;

manufacture our drug candidates;

hire additional clinical, quality control and scientific personnel;

identify additional drug candidates;

acquire or in-license other drugs and technologies; and

add operational, financial and management information systems and personnel, including personnel to support our drug development, any future commercialization efforts and our other operations as a public company.

**Table of Contents**

**Financial Overview**

***Revenue Recognition***

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

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

***Research and Development Expenses***

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

employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;

expenses incurred under agreements with third parties, including contract research organizations, contract manufacturing organizations and consultants that help conduct clinical trials and preclinical studies;

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

facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other operating costs; and

costs associated with preclinical activities and regulatory operations.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, and information provided to us by our vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development.

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

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

establishing an appropriate safety profile with Investigational New Drug-enabling toxicology studies, and ongoing clinical trials;

successful enrollment in, and completion of, clinical trials;

receipt of marketing approvals from applicable regulatory authorities;

establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;

obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our drug candidates;

## **Table of Contents**

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

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

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

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

### ***General and Administrative Expenses***

General and administrative expenses consist primarily of salaries, benefits, travel, and other related costs, including stock-based compensation, for personnel in executive, finance, commercial and administrative functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future to support continued research and development activities, potential commercialization of our drug candidates and increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses.

### ***Interest Expense***

Interest expense consists of interest expense related to the aggregate \$172.5 million principal amount of 3.0% Convertible Senior Notes due 2025 the Company issued in a private offering to qualified institutional buyers in October 2018 (Notes). A portion of the interest expense on the Notes is non-cash expense relating to accretion of the debt discount and amortization of issuance costs. In 2018 we recorded \$2.5 million in interest expense, of which \$1.1 million relates to accrued interest and the remainder to the accretion of the debt discount and amortization of issuance costs of the Notes.

### ***Other Income (Expense)***

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

### **Critical Accounting Policies and Estimates**

Our discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which we have prepared in accordance with United States generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates

## **Table of Contents**

and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenues and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this Form 10-K, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

### ***License and Asset Purchase Agreements***

The Company generates revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of its product candidates. Such agreements may include the transfer of intellectual property rights in the form of licenses, transfer of technological know-how, delivery of drug substances, research and development services, and participation on certain committees with the counterparty. Payments made by the customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of product candidates if they are successfully approved and commercialized.

We adopted Accounting Standards Update (ASU) 2014-09, *Revenue from Contracts with Customers* (ASC 606), as well as subsequent amendments, which were codified in Financial Accounting Standards Board (FASB) Accounting Standard Codification (ASC) 606, on January 1, 2018, using the modified retrospective method for all contracts not completed as of the date of adoption. The reported results for the year ended December 31, 2018 reflect the application of ASC 606 while the reported results for the years ended December 31, 2017 and 2016 were prepared under the guidance of ASC 605, *Revenue Recognition* (ASC 605), which is also referred to herein as (legacy GAAP) or the (previous guidance). The adoption of ASC 606 did not have a material impact on the Company's consolidated financial position, results of operations, stockholder's equity or cash flows as of the adoption date, as no transition adjustment for any of the Company's contracts with customers was required.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, we recognize revenue when our customer obtains control of promised goods or services, in an amount that reflects the consideration which we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assesses whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

If a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize the transaction price allocated to the license as revenue upon transfer of control of the license. We evaluate all other promised goods or services in the agreement to determine if they are distinct. If they are

not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that is distinct. Optional future services where any additional consideration paid to



## **Table of Contents**

us reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights, and are accounted for as performance obligations.

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

We then determine whether the performance obligations or combined performance obligations are satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. We evaluate the measure of progress, as applicable, for each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded within deferred revenue. Contract liabilities within deferred revenue are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

### ***Accrued Research and Development Expenses***

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

We base our expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs and CMOs that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate

the time period over which services will be performed and the level of effort to be

**Table of Contents**

expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepayment accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. Our estimates have not been materially different than amounts actually incurred to date.

**Results of Operations**

The following table summarizes our results of operations for the years ended December 31, 2018, 2017 and 2016:

|                            | <b>Years Ended December 31,</b> |              |              |
|----------------------------|---------------------------------|--------------|--------------|
|                            | <b>2018</b>                     | <b>2017</b>  | <b>2016</b>  |
|                            | <b>(in thousands)</b>           |              |              |
| License and other revenue  | \$ 30,336                       | \$ 1,605     | \$ 154       |
| Operating expenses:        |                                 |              |              |
| Research and development   | 161,372                         | 107,273      | 86,938       |
| General and administrative | 48,847                          | 24,870       | 23,948       |
| Loss from operations       | (179,883)                       | (130,538)    | (110,732)    |
| Other income, net          | 1,502                           | 1,617        | 1,294        |
| Loss before income taxes   | (178,381)                       | (128,921)    | (109,438)    |
| Provision for income taxes | (26)                            | (63)         | (139)        |
| Net loss                   | \$ (178,407)                    | \$ (128,984) | \$ (109,577) |

***Comparison of Years Ended December 31, 2018 and 2017***

***License and Other Revenue.*** Revenue for the year ended December 31, 2018 was \$30.3 million compared to \$1.6 million for the year ended December 31, 2017. We recognized revenue pursuant to an Asset Purchase Agreement (APA) with Biogen MA Inc. (Biogen), a license arrangement with Ono Pharmaceutical Co., Ltd. (Ono) and a government grant arrangement during the year ended December 31, 2018. In comparison, during 2017, our revenue primarily related to \$1.3 million in revenue related to a license agreement with Anivive Lifesciences, Inc.(Anivive), and revenue related to a government grant.

***Research and Development Expense.*** Research and development expense increased by approximately \$54.1 million to \$161.4 million for the year ended December 31, 2018 from \$107.3 million for the year ended December 31, 2017. The increase was primarily related to:

an increase of \$20.4 million in clinical trial costs, primarily related to the selinexor program;

an increase of \$13.5 million in consulting and professional expense related to the preparation and submission of our New Drug Application (NDA) filing;

an increase of \$11.8 million in personnel costs, primarily due to increased headcount and onboarding costs, offset by a decrease of \$2.9 million in stock-based compensation expense;

an increase of \$5.8 million in travel, toxicology study costs and other research and development expenses; and

an increase of \$2.6 million in discovery and occupancy costs.

We expect our research and development expenses to decrease in 2019 as compared with 2018 as we moderate our spending on our development programs and clinical trials, while continuing clinical development

## **Table of Contents**

of selinexor in our lead indications with a focus on regulatory submissions for selinexor. In August 2018, we announced the completion of the rolling submission of an NDA to the Food and Drug Administration (FDA) with a request for accelerated approval for selinexor as a new treatment for patients based on the results from the expanded cohort of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA. We also announced the submission of a Marketing Authorization Application to the European Medicines Agency (EMA) in January 2019 with a request for conditional approval.

In addition, based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with stem cell rescue), including chimeric antigen receptor modified T (CAR-T) cell therapy and intend to work with the FDA to determine the appropriate timeline for the submission. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

*General and Administrative Expense.* General and administrative expense increased by approximately \$23.9 million to approximately \$48.8 million for the year ended December 31, 2018 from approximately \$24.9 million for the year ended December 31, 2017. The increase was primarily related to:

an increase of \$7.3 million in commercial related activities;

an increase of \$6.8 million in personnel costs, primarily due to increased headcount and onboarding costs, offset by a decrease of \$1.2 million in stock-based compensation expense;

an increase of \$4.7 million in consulting and professional costs;

an increase of \$2.9 million in occupancy costs; and

an increase of \$2.3 million in other administrative costs.

We expect our general and administrative expenses to increase in 2019 to support of our expanding operating and commercial activities. However, following our discussions with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor based on the results of the STORM trial, we plan to re-evaluate our planned expenditures during 2019.

*Other income, net.* Other income, net decreased by approximately \$0.1 million to approximately \$1.5 million for the year ended December 31, 2018 from \$1.6 million for the year ended December 31, 2017. The decrease is primarily due to \$2.5 million of interest expense related to the issuance of the Notes offset by a \$2.3 million increase in interest income due to increased returns resulting from a general increase in interest rates and higher investment balances in 2018.

## ***Comparison of Years Ended December 31, 2017 and 2016***

*License and Other Revenue.* We recognized revenue pursuant to a license agreement with Anivive and government grants in 2017 and pursuant to a government grant in 2016. Revenue for the year ended December 31, 2017 was \$1.6 million compared to \$0.2 million for the year ended December 31, 2016.

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

an increase of approximately \$13.3 million in clinical trial costs, primarily related to the selinexor program;

an increase of \$3.0 million in consulting and professional expense;

an increase of \$2.2 million in expenses primarily related to our obligation to pay a portion of upfront fees received from license agreements;

## **Table of Contents**

an increase of \$2.1 million in personnel costs, primarily due to increased headcount and compensation increases, offset by decreased stock-based compensation expense of \$0.9 million; and

an increase of \$0.8 million in travel, toxicology study costs and other expenses;

partially offset by a decrease of \$1.0 million in discovery and occupancy costs.

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

an increase of approximately \$0.7 million in personnel costs, primarily due to increased headcount, offset by a decrease of approximately \$0.9 million in stock-based compensation expense related to equity awards granted to personnel and non-employees; and

an increase in consulting, occupancy and travel costs of \$0.6 million;

partially offset by a decrease of \$0.3 million in other costs.

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

## **Liquidity and Capital Resources**

To date, we have not generated revenues from drug sales. We have financed our operations to date principally through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, issuance of convertible debt and cash generated from our business development activities.

As of December 31, 2018, we had \$330.2 million in cash, cash equivalents and investments.

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

In August 2018, we entered into an open market sale agreement (Open Market Sale Agreement) with Jefferies LLC, as agent, relating to an at-the-market offering, pursuant to which we may issue and sell shares of our common stock, having an aggregate offering price of up to \$75.0 million. To date there have been no sales pursuant to the Open Market Sale Agreement.

## Edgar Filing: Karyopharm Therapeutics Inc. - Form 10-K

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

On May 23, 2018, we entered into a License Agreement (Antengene Agreement) with Antengene Therapeutics Limited, a corporation organized and existing under the laws of Hong Kong (Antengene) and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People's Republic of China, pursuant to which we granted Antengene exclusive rights to develop and



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**Table of Contents**

commercialize, at its own cost, selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications (Oncology Field), as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications (Non-Oncology Field). We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the Oncology Field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the Oncology Field, as well as verdinexor in the Non-Oncology Field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. Under the terms of the Antengene Agreement, we received an upfront cash payment of \$11.7 million and are entitled to receive up to \$105.0 million in milestone payments from Antengene if certain development goals are achieved and up to \$45.0 million in milestone payments from Antengene if certain sales milestones are achieved. We are further eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor in China and Macau, and tiered single- to double-digit royalties based on future net sales of KPT-9274 and verdinexor in the licensed territories. Antengene's obligations under the Antengene Agreement have been guaranteed by Antengene Corporation Co. Ltd.

We are party to a research agreement with the Multiple Myeloma Research Foundation (MMRF). Under this research agreement, we are obligated to make certain payments to MMRF, including if we out-license selinexor. The terms of this research agreement do not apply to eltanexor, KPT-9274 or verdinexor. During the year ended December 31, 2018, we paid approximately \$0.3 million of the Antengene upfront cash payment to MMRF, which reflects the amount owed to MMRF under the Antengene License Agreement transaction. In connection with the transaction pursuant to the license agreement with Ono (Ono License Agreement), we paid to MMRF approximately \$2.0 million of the upfront cash payment from Ono in the year ended December 31, 2017. We will be obligated to pay MMRF a percentage of any milestone payments from Antengene and Ono and a mid-single-digit percentage of any royalty payments from Antengene and Ono. Such payments are recorded within research and development expense in our consolidated statement of operations. As of December 31, 2018, a maximum of \$3.8 million in future obligations are remaining under the MMRF agreement.

On January 24, 2018, we entered into the APA with Biogen, pursuant to which Biogen acquired exclusive worldwide rights to develop and commercialize our oral SINE compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis (ALS). Under the terms of the APA, Biogen purchased KPT-350 and certain related assets and assumed certain related liabilities. We received a one-time upfront payment of \$10.0 million from Biogen and are eligible to receive additional payments of up to \$207.0 million based on the achievement by Biogen of future specified development and commercial milestones. We are also eligible to receive tiered royalty payments that reach low double digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product and the expiration of specified patent protection for the applicable product, determined on a country-by-country basis.

On October 11, 2017 (Ono Effective Date), we entered into the Ono License Agreement, pursuant to which we granted Ono exclusive rights to develop and commercialize, at its own cost, selinexor and eltanexor for the diagnosis, treatment and/or prevention of all human oncology indications in Japan, Republic of Korea, Republic of China (Taiwan) and Hong Kong as well as in the ten Southeast Asian countries currently comprising the Association of Southeast Asian Nations (Ono Territory). Pursuant to the terms of the Ono License Agreement, we received an upfront payment of ¥2.5 billion (US\$21.9 million on the date received), and could receive up to ¥10.15 billion (US\$90.5 million at the exchange rate as of the Ono Effective Date) in milestone payments if certain development goals are achieved and up to ¥9.0 billion (US\$80.2 million at the exchange rate as of the Ono Effective Date) in milestone payments if certain sales milestones are achieved, as well as a low double-digit royalty based on future net sales of selinexor and eltanexor in the Ono Territory.

In December 2015, we entered into a sales agreement (as amended on November 7, 2016 and December 1, 2017, the Sales Agreement) with Cantor Fitzgerald & Co., as sales agent, relating to an at-the-market offering, pursuant to which we issued and sold 9,172,159 shares of our common stock for net proceeds of approximately \$89.1 million. The Sales Agreement was terminated effective August 12, 2018. During the year ended

**Table of Contents**

December 31, 2018, the Company did not sell any shares under the Sales Agreement. During the years ended December 31, 2017 and 2016, the Company sold an aggregate of 3,405,763 shares and 5,645,082 shares, respectively, under the Sales Agreement for net proceeds of approximately \$36,978 and \$50,573, respectively.

At December 31, 2018, we had \$330.2 million in cash, cash equivalents and investments. We have had recurring losses and incurred a loss of \$178.4 million for the year ended December 31, 2018. Net cash used in operations for the year ended December 31, 2018 was \$159.1 million. We expect that cash, cash equivalents and short- and long-term investments at December 31, 2018 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Form 10-K while we establish the commercial infrastructure for a potential launch of selinexor in the United States.

**Cash flows**

The following table provides information regarding our cash flows:

|  | <b>Years Ended December 31,</b> |             |             |
|--|---------------------------------|-------------|-------------|
|  | <b>2018</b>                     | <b>2017</b> | <b>2016</b> |
|  | <b>(in thousands)</b>           |             |             |
| Net cash used in operating activities                | \$ (159,117)                    | \$ (73,717) | \$ (84,391) |
| Net cash (used in) provided by investing activities  | (107,664)                       | 17,108      | 24,595      |
| Net cash provided by financing activities            | 316,109                         | 75,743      | 51,164      |
| Effect of exchange rate changes                      | (78)                            | 211         | (66)        |
| Net increase (decrease) in cash and cash equivalents | \$ 49,250                       | \$ 19,345   | \$ (8,698)  |

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

Net cash used in operating activities was \$159.1 million during the year ended December 31, 2018 compared to \$73.7 million during the year ended December 31, 2017. Net cash used in operating activities in both periods resulted primarily from our net losses adjusted for non-cash charges and changes in the components of working capital. The increase in cash used in operating activities during the year ended December 31, 2018 compared to the year ended December 31, 2017 was driven primarily by a \$49.4 million increase in our net loss due to an increase in our operating expenses, an \$8.0 million decrease in deferred revenue primarily attributable to recognizing \$19.7 million of the upfront cash payment received under the Ono License Agreement in 2017 and partially offset by the \$11.7 million upfront cash payment received under the Antengene License Agreement in June and changes in the components of working capital.

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

***Net Cash (Used in) Provided by Investing Activities***

Net cash used in investing activities increased by \$124.8 million during the year ended December 31, 2018 compared to the year ended December 31, 2017. The increase was primarily related to an increase of \$144.4 million in the purchases of investments, partially offset by an increase of \$22.0 million in proceeds from maturities of investments.

## **Table of Contents**

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

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

Net cash provided by financing activities was \$316.1 million during the year ended December 31, 2018 compared to \$75.7 million during the year ended December 31, 2017. The \$240.4 million increase primarily reflects \$166.9 million in net proceeds from the issuance of the Notes in October 2018 and \$145.7 million in net proceeds from our follow-on offering of common stock in May 2018 as compared to \$37.0 million in net proceeds from the sale of common stock as part of the at-the-market offering during 2017 and \$37.9 million in net proceeds from our follow-on offering of common stock in April 2017.

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

### **Funding requirements**

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical trials of and as we seek marketing approval for, selinexor and our other drug candidates. In addition, if we obtain marketing approval for any of our drug candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time for any such drug. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We expect that cash, cash equivalents and short- and long-term investments at December 31, 2018 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Form 10-K while we establish the commercial infrastructure for a potential launch of selinexor in the United States. Our future capital requirements will depend on many factors, including:

the progress and results of our current and planned clinical trials of selinexor;

the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our other drug candidates;

the costs, timing and outcome of regulatory review of our drug candidates;

our ability to establish and maintain collaborations on favorable terms, if at all;

the success of any collaborations that we may enter into with third parties;

the extent to which we acquire or in-license other drugs and technologies;

**Table of Contents**

the costs of future commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our drug candidates for which we receive marketing approval, to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time;

the amount of revenue, if any, received from commercial sales of our drug candidates, should any of our drug candidates receive marketing approval; and

the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that may not be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

**Contractual Obligations**

As of December 31, 2018, we had the following contractual obligations:

| Contractual Obligations            | Total      | Payments Due by Period |              |              |                   |
|------------------------------------|------------|------------------------|--------------|--------------|-------------------|
|                                    |            | Less than 1 Year       | 1 to 3 Years | 3 to 5 Years | More than 5 Years |
|                                    |            | (in thousands)         |              |              |                   |
| Operating lease obligations(1)     | \$ 23,431  | \$ 3,046               | \$ 6,485     | \$ 7,165     | \$ 6,735          |
| Purchase obligations(2)            |            |                        |              |              |                   |
| Convertible senior notes           | 208,725    | 5,175                  | 10,350       | 10,350       | 182,850           |
| Total contractual cash obligations | \$ 232,156 | \$ 8,221               | \$ 16,835    | \$ 17,515    | \$ 189,585        |

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

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

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

*Multiple Myeloma Research Foundation*

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



## **Table of Contents**

If we, our affiliates, licensees or transferees commercialize products incorporating a program invention or program intellectual property, which we call research program products, we would be obligated to pay to MMRF mid-single-digit royalties as a percentage of worldwide net sales of research program products, including selinexor, sold by us, our affiliates, licensees or transferees. If we out-license rights to a research program product, we are obligated to pay MMRF a percentage of certain payments we receive from our licensee for the grant of such rights. If we sell all or substantially all of our assets to one or more third parties who were not our stockholders on the effective date of the agreement, or if one or more third parties acquire more than fifty percent of our equity and payments are made directly to our stockholders for the sale of their shares of our stock, each of which we call a change of control, we will be obligated to pay to MMRF a percentage of the value we or our shareholders receive in connection with such change of control. The maximum aggregate amount we may be obligated to pay to MMRF for royalties, out-licensing our rights or as a result of a change of control is \$6.0 million, of which \$2.3 million has been paid through December 31, 2018 in connection with the Antengene License Agreement and the Ono License Agreement.

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

## **Off-Balance Sheet Arrangements**

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

## **Inflation**

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

## **Recently Issued Accounting Pronouncements**

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

## **Item 7A. Quantitative and Qualitative Disclosures about Market Risk**

We are exposed to market risk related to changes in interest rates. As of December 31, 2018 and 2017, we had cash, cash equivalents, restricted cash and investments of \$330.9 million and \$176.4 million, respectively. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term maturities of our cash equivalents and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our cash equivalents or investment portfolio.

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

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

## **Table of Contents**

### **Item 8. Financial Statements and Supplementary Data**

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appears on pages 127 through 132 of this Annual Report on Form 10-K.

### **Item 9A. Controls and Procedures**

#### ***Evaluation of Disclosure Controls and Procedures***

The Company has established disclosure controls and procedures designed to ensure that information required to be disclosed in the reports that the Company files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the rules and forms prescribed by the Securities and Exchange Commission and is accumulated and communicated to management, including the principal executive officer (our Chief Executive Officer) and principal financial officer (our Vice President, Finance and Assistant Treasurer), to allow timely decisions regarding required disclosure.

Our management, under the supervision and with the participation of our Chief Executive Officer and Vice President, Finance and Assistant Treasurer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Management recognizes that any disclosure controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives. Our disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on such evaluation, our Chief Executive Officer and Vice President, Finance and Assistant Treasurer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2018.

#### ***Management's Annual Report on Internal Control Over Financial Reporting***

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate. Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

Under the supervision and with the participation of management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the 2013 framework in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under that framework, management concluded that our internal control over financial reporting was effective as of December 31, 2018.

Our independent registered public accounting firm that audited the financial statements included in this Annual Report on Form 10-K has issued an attestation report on our internal control over financial reporting, which is included below.

#### ***Changes in Internal Control over Financial Reporting***

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

**Table of Contents**

**Report of Independent Registered Public Accounting Firm**

To the Shareholders and the Board of Directors of Karyopharm Therapeutics Inc.

**Opinion on Internal Control over Financial Reporting**

We have audited Karyopharm Therapeutics Inc.'s internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Karyopharm Therapeutics Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the 2018 consolidated financial statements of the Company and our report dated February 28, 2019 expressed an unqualified opinion thereon.

**Basis for Opinion**

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

**Definition and Limitations of Internal Control Over Financial Reporting**

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 28, 2019

**Table of Contents**

**Item 9B. Other Information**

None.

**Table of Contents**

**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 2019 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2019 Proxy Statement. We expect to file our 2019 Proxy Statement with the SEC within 120 days of December 31, 2018.

**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 2019 Proxy Statement and is incorporated herein by reference.

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

Karyopharm Therapeutics Inc.

Attention: Investor Relations

85 Wells Avenue, 2<sup>nd</sup> Floor

Newton, MA 02459

We will post to our website any amendments to the Code of Business Conduct and Ethics and any waivers that are required to be disclosed by the rules of either the SEC or Nasdaq.

**Item 11. Executive Compensation**

The information required by this Item 11 of Form 10-K regarding executive compensation will be included in our 2019 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 2019 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 2019 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 2019 Proxy Statement and is incorporated herein by reference.

**Table of Contents****PART IV****Item 15. Exhibits and Financial Statement Schedules****(a)(1) Financial Statements**

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

|   | <b>Page<br/>number</b> |
|---|------------------------|
| <u>Report of Independent Registered Public Accounting Firm</u>  | 128                    |
| <u>Consolidated Balance Sheets as of December 31, 2018 and 2017</u>   | 129                    |
| <u>Consolidated Statements of Operations for the years ended December 31, 2018, 2017 and 2016</u>           | 130                    |
| <u>Consolidated Statements of Comprehensive Loss for the years ended December 31, 2018, 2017 and 2016</u>   | 131                    |
| <u>Consolidated Statements of Stockholders' Equity for the years ended December 31, 2018, 2017 and 2016</u> | 132                    |
| <u>Consolidated Statements of Cash Flows for the years ended December 31, 2018, 2017 and 2016</u>           | 133                    |
| <u>Notes to Consolidated Financial Statements</u>   | 134                    |
| <b>(a)(2) Financial Statement Schedules</b>   |                        |

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

**(a)(3) Exhibits**

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

**Item 16. Form 10-K Summary**

None.

**Table of Contents**

**Report of Independent Registered Public Accounting Firm**

To the Shareholders and

the Board of Directors of Karyopharm Therapeutics Inc.

**Opinion on the Financial Statements**

We have audited the accompanying consolidated balance sheets of Karyopharm Therapeutics Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders equity, and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 28, 2019 expressed an unqualified opinion thereon.

**Basis for Opinion**

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.

Boston, Massachusetts

February 28, 2019



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

(in thousands, except share and per share amounts)

|  | <b>December 31,<br/>2018</b> | <b>December 31,<br/>2017</b> |
|--|------------------------------|------------------------------|
| <b>ASSETS</b>  |                              |                              |
| Current assets:  |                              |                              |
| Cash and cash equivalents  | \$ 118,021                   | \$ 68,997                    |
| Short-term investments   | 210,178                      | 77,472                       |
| Prepaid expenses and other current assets  | 6,413                        | 1,754                        |
| Restricted cash  |                              | 200                          |
| <b>Total current assets</b>  | <b>334,612</b>               | <b>148,423</b>               |
| Property and equipment, net  | 3,863                        | 2,185                        |
| Long-term investments  | 2,001                        | 29,396                       |
| Restricted cash  | 716                          | 290                          |
| <b>Total assets</b>  | <b>\$ 341,192</b>            | <b>\$ 180,294</b>            |
| <b>LIABILITIES AND STOCKHOLDERS EQUITY</b>   |                              |                              |
| Current liabilities:   |                              |                              |
| Accounts payable   | \$ 4,332                     | \$ 5,665                     |
| Accrued expenses   | 32,493                       | 21,445                       |
| Deferred revenue   | 9,362                        | 21,921                       |
| Deferred rent  | 390                          | 303                          |
| Other current liabilities  | 327                          | 133                          |
| <b>Total current liabilities</b>   | <b>46,904</b>                | <b>49,467</b>                |
| Convertible senior notes   | 102,664                      |                              |
| Deferred revenue, net of current portion   | 4,532                        |                              |
| Deferred rent, net of current portion  | 3,922                        | 1,363                        |
| <b>Total liabilities</b>   | <b>158,022</b>               | <b>50,830</b>                |
| Commitments and contingencies (Note 8)   |                              |                              |
| Stockholders equity:   |                              |                              |
| Preferred stock, \$0.0001 par value; 5,000,000 shares authorized; none issued and outstanding  |                              |                              |
| Common stock, \$0.0001 par value; 100,000,000 shares authorized; 60,829,308 and 49,533,150 shares issued and outstanding at December 31, 2018 and 2017, respectively | 6                            | 5                            |

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|   |                   |                   |
|---|-------------------|-------------------|
| Additional paid-in capital                        | 857,156           | 625,017           |
| Accumulated other comprehensive loss              | (244)             | (217)             |
| Accumulated deficit                               | (673,748)         | (495,341)         |
| <b>Total stockholders' equity</b>                 | <b>183,170</b>    | <b>129,464</b>    |
| <b>Total liabilities and stockholders' equity</b> | <b>\$ 341,192</b> | <b>\$ 180,294</b> |

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

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

|  | <b>For the Years Ended December 31,</b> |              |              |
|--|---|--------------|--------------|
|  | <b>2018</b>                             | <b>2017</b>  | <b>2016</b>  |
| License and other revenue  | \$ 30,336                               | \$ 1,605     | \$ 154       |
| Operating expenses:  |   |              |              |
| Research and development   | 161,372                                 | 107,273      | 86,938       |
| General and administrative   | 48,847                                  | 24,870       | 23,948       |
| Total operating expenses   | 210,219                                 | 132,143      | 110,886      |
| Loss from operations   | (179,883)                               | (130,538)    | (110,732)    |
| Other income (expense):  |   |              |              |
| Interest income  | 4,028                                   | 1,698        | 1,284        |
| Interest expense   | (2,493)                                 |              |              |
| Other (expense) income   | (33)                                    | (81)         | 10           |
| Total other income, net  | 1,502                                   | 1,617        | 1,294        |
| Loss before income taxes   | (178,381)                               | (128,921)    | (109,438)    |
| Provision for income taxes   | (26)                                    | (63)         | (139)        |
| Net loss   | \$ (178,407)                            | \$ (128,984) | \$ (109,577) |
| Net loss per share basic and diluted   | \$ (3.14)                               | \$ (2.81)    | \$ (2.92)    |
| Weighted-average number of common shares outstanding used<br>in net loss per share basic and diluted | 56,799,699                              | 45,899,784   | 37,523,051   |

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

**Table of Contents**

**Karyopharm Therapeutics Inc.**  
**Consolidated Statements of Comprehensive Loss**

(in thousands)

|   | <b>For the Years Ended December 31,</b> |              |              |
|---|---|--------------|--------------|
|   | <b>2018</b>                             | <b>2017</b>  | <b>2016</b>  |
| Net loss                                | \$ (178,407)                            | \$ (128,984) | \$ (109,577) |
| Other comprehensive income (loss):      |   |              |              |
| Unrealized gain (loss) on investments   | 39                                      | (97)         | 34           |
| Foreign currency translation adjustment | (66)                                    | 154          | (26)         |
| Comprehensive loss                      | \$ (178,434)                            | \$ (128,927) | \$ (109,569) |

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



Table of Contents**Karyopharm Therapeutics Inc.****Consolidated Statements of Stockholders Equity**

(in thousands, except share amounts)

|  | Common Shares |        | Accumulated                      |                                |                        | Total<br>Stockholders<br>Equity<br>(Deficit) |
|--|---------------|--------|----------------------------------|--------------------------------|------------------------|--|
|  | Shares        | Amount | Additional<br>Paid-In<br>Capital | Other<br>Comprehensive<br>Loss | Accumulated<br>Deficit |  |
| <b>Balance at December 31, 2015</b>  | 35,864,765    | \$ 4   | \$ 455,170                       | \$ (282)                       | \$ (256,527)           | \$ 198,365                                   |
| Vesting of restricted stock  | 262,125       |        |                                  |                                |                        |  |
| Settlements of restricted stock units<br>for tax withholding obligations                 | (6,526)       |        | (39)                             |                                |                        | (39)   |
| Exercise of stock options and shares<br>issued under the employee stock<br>purchase plan | 122,383       |        | 630                              |                                |                        | 630  |
| Stock-based compensation expense   |               |        | 22,283                           |                                |                        | 22,283                                       |
| Issuance of common stock, net of<br>issuance costs of \$1,530                            | 5,645,082     |        | 50,573                           |                                |                        | 50,573                                       |
| Unrealized gain on investments   |               |        |                                  | 34                             |                        | 34   |
| Foreign currency translation<br>adjustment   |               |        |                                  | (26)                           |                        | (26)   |
| Net loss   |               |        |                                  | 0                              | (109,577)              | (109,577)                                    |
| <b>Balance at December 31, 2016</b>  | 41,887,829    | 4      | 528,617                          | (274)                          | (366,104)              | 162,243                                      |
| Cumulative effect adjustment for<br>adoption of new accounting guidance                  |               |        | 253                              |                                | (253)                  |  |
| Vesting of restricted stock  | 182,496       |        |                                  |                                |                        |  |
| Exercise of stock options and shares<br>issued under the employee stock<br>purchase plan | 154,623       |        | 858                              |                                |                        | 858  |
| Stock-based compensation expense   |               |        | 20,405                           |                                |                        | 20,405                                       |
| Issuance of common stock, net of<br>issuance costs of \$1,060                            | 7,308,202     | 1      | 74,884                           |                                |                        | 74,885                                       |
| Unrealized loss on investments   |               |        |                                  | (97)                           |                        | (97)   |
| Foreign currency translation<br>adjustment   |               |        |                                  | 154                            |                        | 154  |
| Net loss   |               |        |                                  |                                | (128,984)              | (128,984)                                    |
| <b>Balance at December 31, 2017</b>  | 49,533,150    | 5      | 625,017                          | (217)                          | (495,341)              | 129,464                                      |
| Vesting of restricted stock  | 113,800       |        |                                  |                                |                        |  |
| Exercise of stock options and shares<br>issued under the employee stock<br>purchase plan | 656,934       |        | 3,519                            |                                |                        | 3,519  |

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|   |                   |             |                   |                 |                     |                   |
|---|-------------------|-------------|-------------------|-----------------|---------------------|-------------------|
| Stock-based compensation expense                            |                   |             | 17,275            |                 |                     | 17,275            |
| Issuance of common stock, net of issuance costs of \$231    | 10,525,424        | 1           | 145,704           |                 |                     | 145,705           |
| Equity component of 2025 Notes                              |                   |             | 67,850            |                 |                     | 67,850            |
| Equity component of deferred financing costs for 2025 notes |                   |             | (2,209)           |                 |                     | (2,209)           |
| Unrealized gain on investments                              |                   |             |                   | 39              |                     | 39                |
| Foreign currency translation adjustment                     |                   |             |                   | (66)            |                     | (66)              |
| Net loss  |                   |             |                   |                 | (178,407)           | (178,407)         |
| <b>Balance at December 31, 2018</b>                         | <b>60,829,308</b> | <b>\$ 6</b> | <b>\$ 857,156</b> | <b>\$ (244)</b> | <b>\$ (673,748)</b> | <b>\$ 183,170</b> |

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

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

|  | <b>For the Year Ended December 31,</b> |              |              |
|--|--|--------------|--------------|
|  | <b>2018</b>                            | <b>2017</b>  | <b>2016</b>  |
| <b>Operating activities</b>  |  |              |              |
| Net loss   | \$ (178,407)                           | \$ (128,984) | \$ (109,577) |
| Adjustments to reconcile net loss to net cash used in operating activities:                      |  |              |              |
| Depreciation and amortization  | 735                                    | 713          | 717          |
| Net amortization of premiums and discounts on investments  | 29                                     | 1,187        | 1,199        |
| Stock-based compensation expense   | 17,275                                 | 20,405       | 22,283       |
| Amortization of debt discount and issuance costs   | 1,420                                  |              |              |
| Change in operating assets and liabilities:  |  |              |              |
| Prepaid expenses and other current assets  | (4,663)                                | 342          | (120)        |
| Accounts payable   | (1,380)                                | 909          | 945          |
| Accrued expenses and other liabilities   | 11,255                                 | 10,070       | 368          |
| Deferred revenue   | (8,027)                                | 21,921       |              |
| Deferred rent  | 2,646                                  | (280)        | (206)        |
| Net cash used in operating activities  | (159,117)                              | (73,717)     | (84,391)     |
| <b>Investing activities</b>  |  |              |              |
| Purchases of property and equipment  | (2,363)                                | (62)         | (70)         |
| Proceeds from maturities of investments  | 137,510                                | 115,544      | 159,365      |
| Purchases of investments   | (242,811)                              | (98,374)     | (134,700)    |
| Net cash (used in) provided by investing activities  | (107,664)                              | 17,108       | 24,595       |
| <b>Financing activities</b>  |  |              |              |
| Proceeds from issuance of convertible senior notes, net of issuance costs                        | 166,885                                |              |              |
| Proceeds from issuance of common stock, net of issuance costs                                    | 145,705                                | 74,885       | 50,573       |
| Proceeds from the exercise of stock options and shares issued under employee stock purchase plan | 3,519                                  | 858          | 630          |
| Settlements of restricted stock units for tax withholding obligations                            |  |              | (39)         |
| Net cash provided by financing activities  | 316,109                                | 75,743       | 51,164       |
| Effect of exchange rate on cash, cash equivalents and restricted cash                            | (78)                                   | 211          | (66)         |
| Net increase (decrease) in cash, cash equivalents and restricted cash                            | 49,250                                 | 19,345       | (8,698)      |
| Cash, cash equivalents and restricted cash at beginning of period                                | 69,487                                 | 50,142       | 58,840       |
| Cash, cash equivalents and restricted cash end of period   | \$ 118,737                             | \$ 69,487    | \$ 50,142    |

**Reconciliation of cash, cash equivalents and restricted cash reported  
within the consolidated balance sheets**

|  |            |           |           |
|--|------------|-----------|-----------|
| Cash and cash equivalents                        | \$ 118,021 | \$ 68,997 | \$ 49,663 |
| Short-term restricted cash                       |            | 200       |           |
| Long-term restricted cash                        | 716        | 290       | 479       |
| Total cash, cash equivalents and restricted cash | \$ 118,737 | \$ 69,487 | \$ 50,142 |

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

**Table of Contents**

**Karyopharm Therapeutics Inc.**

**Notes to Consolidated Financial Statements**

**(in thousands, except share and per share amounts)**

**1. Organization and Operations**

***The Company***

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

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

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

The Company has generated an accumulated deficit of \$673,748 since inception. The Company has financed its operations to date primarily through private placements of its preferred stock, proceeds from its initial public offering and follow-on offerings of common stock, issuance of convertible debt and cash generated from its business development activities. The Company has not completed development of any product candidate and has devoted substantially all of its financial resources and efforts to research and development, including preclinical and clinical development. The Company expects to continue to incur significant expenses and operating losses for at least the foreseeable future. The Company expects that its cash, cash equivalents and investments at December 31, 2018 will be sufficient to fund current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of these financial statements while it establishes the commercial infrastructure for a potential launch of selinexor in the United States.

**2. Summary of Significant Accounting Policies**

***Basis of Presentation***

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

***Segment Information***

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment, which is the business of discovering, developing and commercializing drugs to treat cancer and certain other major

diseases. All of the Company's revenues to date have been derived in the United States. All material long-lived assets of the Company reside in the United States.

*Use of Estimates*

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period.

## **Table of Contents**

On an ongoing basis, the Company's management evaluates its estimates, including estimates related to clinical trial accruals, stock-based compensation expense, and reported amounts of expenses during the reported period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Although the Company regularly assesses these estimates, actual results could differ from those estimates. Changes in estimates are recorded in the period in which they become known.

### ***Principles of Consolidation***

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

### ***Cash and Cash Equivalents***

Cash and cash equivalents consist primarily of demand deposit accounts and deposits in short-term money market funds. Cash equivalents are stated at cost, which approximates fair value. The Company considers all highly liquid investments with maturities of three months or less from the date of purchase to be cash equivalents. The Company does not hold any money market funds with significant liquidity restrictions that would be required to be excluded from cash equivalents.

### ***Investments***

The Company determines the appropriate classification of its investments in debt securities at the time of purchase. All of the Company's securities are classified as available-for-sale and are reported in short-term investments or long-term investments based on maturity dates and whether such assets are reasonably expected to be realized in cash or sold or consumed during the normal cycle of business. Available-for-sale investments are recorded at fair value, with unrealized gains or losses included in Accumulated Other Comprehensive Loss on the Company's Consolidated Balance Sheets, exclusive of other-than-temporary impairment losses, if any. Short-term and long-term investments are composed of corporate debt securities, commercial paper, U.S. government agency securities and certificates of deposit.

### ***Concentrations of Credit Risk and Off-Balance Sheet Risk***

Financial instruments which potentially subject the Company to credit risk consist primarily of cash, cash equivalents and investments. The Company holds these investments in highly rated financial institutions, and, by policy, limits the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

### ***Fair Value Measurements***

Financial instruments, including cash, restricted cash, prepaid expenses and other current assets, accounts payable and accrued expenses, are presented in the consolidated financial statements at amounts that approximate fair value at

December 31, 2018 and 2017.



**Table of Contents**

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1 inputs Quoted prices in active markets for identical assets or liabilities

Level 2 inputs Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly

Level 3 inputs Unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability

The Company's cash equivalents are composed of money market funds. The Company measures these investments at fair value. The fair value of cash equivalents is determined based on Level 1 inputs.

Items classified as Level 2 within the valuation hierarchy consist of commercial paper, corporate debt securities, U.S. government agency securities and certificates of deposit. The Company estimates the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources. These pricing sources utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include market pricing based on real-time trade data for the same or similar securities, issuer credit spreads, benchmark yields, and other observable inputs. The Company validates the prices provided by its third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

The following table presents information about the Company's financial assets that have been measured at fair value at December 31, 2018 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

| <b>Description</b>                    | <b>Total</b> | <b>Quoted Prices<br/>in Active<br/>Markets<br/>(Level 1)</b> | <b>Significant<br/>Other<br/>Observable<br/>Inputs<br/>(Level 2)</b> | <b>Significant<br/>Unobservable<br/>Inputs<br/>(Level 3)</b> |
|---------------------------------------|--------------|--|--|--|
| <b>Financial assets</b>               |              |  |  |  |
| Cash equivalents:                     |              |  |  |  |
| Money market funds                    | \$ 76,881    | \$ 76,881  | \$   | \$   |
| Investments:                          |              |  |  |  |
| Current:                              |              |  |  |  |
| Corporate debt securities             | 143,079      |  | 143,079  |  |
| Commercial paper                      | 43,978       |  | 43,978   |  |
| U.S. government and agency securities | 19,124       |  | 19,124   |  |
| Certificate of deposit                | 3,997        |  | 3,997  |  |
| Non-current:                          |              |  |  |  |

|  |            |    |        |            |
|--|------------|----|--------|------------|
| Corporate debt securities (one to two year maturity) | 2,001      |    | 2,001  |            |
|  | \$ 289,060 | \$ | 76,881 | \$ 212,179 |
|  |            |    |        | \$         |

**Table of Contents**

The following table presents information about the Company's financial assets that have been measured at fair value at December 31, 2017 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

| <b>Description</b>                                      | <b>Total</b> | <b>Quoted Prices<br/>in Active<br/>Markets<br/>(Level 1)</b> | <b>Significant<br/>Other<br/>Observable<br/>Inputs<br/>(Level 2)</b> | <b>Significant<br/>Unobservable<br/>Inputs<br/>(Level 3)</b> |
|---|--------------|--|--|--|
| <b>Financial assets</b>                                 |              |  |  |  |
| Cash equivalents:                                       |              |  |  |  |
| Money market funds                                      | \$ 41,805    | \$ 41,805  | \$   | \$   |
| Investments:  |              |  |  |  |
| Current:  |              |  |  |  |
| Corporate debt securities                               | 66,253       |  | 66,253   |  |
| Commercial paper  | 6,720        |  | 6,720  |  |
| Certificates of deposit                                 | 2,500        |  | 2,500  |  |
| U.S. government and agency securities                   | 1,999        |  | 1,999  |  |
| Non-current:  |              |  |  |  |
| Corporate debt securities (one to two<br>year maturity) | 26,916       |  | 26,916   |  |
| U.S. government securities and agency<br>securities     | 2,480        |  | 2,480  |  |
|   | \$ 148,673   | \$ 41,805  | \$ 106,868   | \$   |

***Property and Equipment, net***

Property and equipment are recorded at cost, less accumulated depreciation. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, generally three to five years. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful economic lives of the related assets. Expenditures for maintenance and repairs are charged to expense while the costs of significant improvements are capitalized. Upon retirement or sale, the cost of the assets disposed of and the related accumulated depreciation are eliminated from the balance sheets and any related gains or losses are reflected in the consolidated statements of operations.

***Long-Lived Assets***

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

***Deferred Rent***

Deferred rent consists of rent escalation payment terms, tenant improvement allowances and other incentives received from landlords related to the Company's operating leases. Rent escalation represents the difference between actual operating lease payments due and straight-line rent expense, which is recorded by the Company over the term of the lease. Tenant improvement allowances and other incentives are recorded as deferred rent and amortized as a reduction of periodic rent expense, over the term of the applicable lease.

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**Table of Contents*****Revenue Recognition***

The Company adopted Accounting Standards Update ( ASU ) 2014-09, *Revenue from Contracts with Customers* (ASC 606), as well as subsequent amendments, which were codified in Financial Accounting Standards Board ( FASB ) Accounting Standard Codification ( ASC ) 606, on January 1, 2018, using the modified retrospective method for all contracts not completed as of the date of adoption. The reported results for the year ended December 31, 2018 reflect the application of ASC 606 while the reported results for the years ended December 31, 2017 and 2016 were prepared under the guidance of ASC 605, *Revenue Recognition* (ASC 605), which is also referred to herein as legacy GAAP or the previous guidance . The adoption of ASC 606 did not have a material impact on the Company s consolidated financial position, results of operations, stockholder s equity or cash flows as of the adoption date, as no transition adjustment for any of the Company s contracts with customers was required.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company generates revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of its product candidates. Such agreements may include the transfer of intellectual property rights in the form of licenses, transfer of technological know-how, delivery of drug substances, research and development services, and participation on certain committees with the counterparty. Payments made by the customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of product candidates if they are successfully approved and commercialized.

If a license to the Company s intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes the transaction price allocated to the license as revenue upon transfer of control of the license. The Company evaluates all other promised goods or services in the agreement to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that is distinct. Optional future services where any additional consideration paid to the Company reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights, and are accounted for as performance obligations.

The Company utilizes judgment to determine the transaction price. In connection therewith, the Company evaluates contingent milestones at contract inception to estimate the amount which is not probable of a material reversal to include in the transaction price using the most likely amount method. Milestone payments that are not within the control of the Company, such as regulatory approvals, are not considered probable of being achieved until those approvals are received and therefore the variable consideration is constrained. The transaction price is then allocated

to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end

## **Table of Contents**

of each reporting period, the Company re-evaluates the probability of achieving development milestone payments which may not be subject to a material reversal and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

The Company then determines whether the performance obligations or combined performance obligations are satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. The Company evaluates the measure of progress, as applicable, for each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded within deferred revenue. Contract liabilities within deferred revenue are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

## ***Research and Development Expenses***

Research and development costs are charged to expense as incurred and include, but are not limited to:

employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;

expenses incurred under agreements with contract research organizations, contract manufacturing organizations and consultants that help conduct clinical trials and preclinical studies;

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

facility, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies; and

costs associated with preclinical activities and regulatory operations.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, or information provided to the Company by its vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are accordingly reflected in the financial statements as prepaid or accrued research and development.

***Comprehensive Loss***

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

***Foreign Currency Transactions***

The functional currency of the Company's subsidiaries in Germany and Israel are the Euro and Shekel, respectively. Foreign currency transaction gains and losses are recorded in the consolidated statement of operations. Net foreign exchange (losses) gains of \$(27), \$(62) and \$10 were recorded in other income (expense) for the years ended December 31, 2018, 2017 and 2016, respectively.



## **Table of Contents**

### ***Income Taxes***

The Company uses the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and the tax reporting basis of assets and liabilities and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. The Company provides a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax assets will be realized. The Company has evaluated available evidence and concluded that the Company may not realize the benefit of its deferred tax assets; therefore, a valuation allowance has been established for the full amount of the deferred tax assets. The Company recognizes interest and/or penalties related to income tax matters in income tax expense. The Company's foreign tax provision pertains to foreign income taxes due at its German subsidiary which operates on a cost plus profit margin basis.

The Tax Cuts and Jobs Act of 2017 ( TCJA ) resulted in significant changes to the U.S. corporate income tax system. For additional details regarding this act, see Note 12, *Income Taxes* .

### ***Accounting for Stock-Based Compensation***

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

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

Compensation expense related to awards to employees is recognized on a straight-line basis based on the grant date fair value over the requisite service period of the award, which is generally the vesting term. Stock-based compensation expense for awards granted to non-employees is adjusted as the award vests to reflect the current fair value of such awards and is recognized using an accelerated attribution model. Forfeitures are recognized as they occur.

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

### ***Net Loss Per Share***

Basic and diluted net loss per common share is calculated by dividing net loss by the weighted-average number of common shares outstanding for the period, without consideration for common stock equivalents. The Company's

potential dilutive shares, stock options, unvested restricted stock and restricted stock units are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

**Table of Contents**

The following potentially dilutive securities were excluded from the calculation of diluted net loss per share due to their anti-dilutive effect at December 31, 2018, 2017 and 2016 (in common stock equivalent shares):

|                                 | <b>December 31,</b> |             |             |
|---------------------------------|---------------------|-------------|-------------|
|                                 | <b>2018</b>         | <b>2017</b> | <b>2016</b> |
| Outstanding stock options       | 8,917,084           | 7,019,083   | 5,574,179   |
| Unvested restricted stock units | 25,000              | 253,100     | 214,300     |

The Company has the option to settle the conversion obligation for the Convertible Notes in cash, shares or any combination of the two. As the Convertible Notes are not convertible as of December 31, 2018, they are not participating securities and they will not have an impact on the calculation of basic earnings or loss per share. Based on the Company's net loss position, there is no impact on the calculation of dilutive loss per share during the year ended December 31, 2018.

**Recently Adopted Accounting Standards**

As detailed above, the Company adopted ASC 606 on January 1, 2018. Under the modified retrospective transition method, the Company applied ASC 606 to all contracts within scope as of January 1, 2018. Under the practical expedient concerning contract modifications contained in the transitional provisions of ASC 606, the Company has not retrospectively restated its contracts for modifications prior to the earliest period presented, and instead has reflected the aggregate effect of all modifications when identifying the satisfied and unsatisfied performance obligations, determining the transaction price and allocating the transaction price. Qualitatively, the effect of applying this practical expedient is not material to the periods presented in the consolidated financial statements. As more fully discussed in Note 9, Asset Purchase and License Agreements, only the Company's arrangement with Ono Pharmaceutical Co., Ltd. was determined to have unsatisfied performance obligations as of the adoption date. However, the pattern of revenue recognition was not affected and, therefore, no transition adjustment was recorded to the opening balance of accumulated deficit on January 1, 2018. All other agreements subject to transition, which only included the Company's arrangement with Anivive Lifesciences Inc., were unaffected by the adoption of ASC 606 in all periods presented in the consolidated financial statements through application of the modified retrospective transition method.

In August 2016, the FASB issued ASU 2016-15, *Classification of Certain Cash Receipts and Cash Payments* (ASU 2016-15). This standard addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. The Company adopted ASU 2016-05 effective January 1, 2018 and the adoption did not have a material impact on the Company's statements of cash flows.

In October 2016, the FASB issued ASU No. 2016-16, *Accounting for Income Taxes: Intra-Entity Asset Transfers of Assets Other than Inventory (Topic 740)*. Topic 740 eliminates the ability to defer the tax expense related to intra-entity asset transfers other than inventory. Under this standard, entities recognize the income tax consequences on an intra-entity transfer of an asset other than inventory when the transfer occurs. The Company adopted Topic 740 effective January 1, 2018 and the adoption did not have a material impact on the Company's financial position or results of operations.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash*. This standard requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash

equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The Company adopted this standard effective January 1, 2018 and reclassified restricted cash in the statements of cash flows to be included in the cash and cash equivalents balance. The standard resulted in the reclassification of \$490, \$479 and \$482 into cash, cash equivalents and restricted cash within the beginning of period balance on the consolidated statements of cash flows for the years ended

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**Table of Contents**

December 31, 2018, 2017 and 2016, respectively. This adoption also resulted in an immaterial adjustment to the effect of exchange rate on cash, cash equivalents and restricted cash during the year ended December 31, 2018.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting* ( ASU 2017-09 ). ASU 2017-09 provides clarification on when modification accounting should be used for changes to the terms or conditions of a share-based payment award. This ASU does not change the accounting for modifications but clarifies that modification accounting guidance should only be applied if there is a change to the value, vesting conditions, or award classification and would not be required if the changes are considered non-substantive. The Company adopted this standard effective January 1, 2018 and the adoption did not have a material impact on the Company's consolidated financial statements.

On December 22, 2017, the TCJA was enacted and led to significant changes to U.S. tax law. Also on December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118 ( SAB 118 ), allowing companies to record the effects of the TCJA on a provisional basis during a measurement period not to extend beyond one year of the enactment date. SAB 118 was codified into ASC 740, *Income Taxes*, by ASU 2018-05. The Company recorded a reduction to its deferred tax asset for \$42,763 and a corresponding reduction to its valuation allowance related to implementing applicable provisions of the TCJA during the year ended December 31, 2017. Through December 22, 2018, there was no further material information or change in estimates related to the provisional amount recognized during the year ended December 31, 2017, and, as such, the Company finalized the provisional amounts recorded under SAB 118 with immaterial changes recognized.

***Recently Issued Accounting Standards***

On August 17, 2018, the SEC issued an amendment to Rule 3-04 of Regulation S-X, which extended the annual disclosure requirement of reporting changes in stockholders' equity to interim periods. Such disclosures are to be provided in a note to the financial statements or in a separate financial statement and requires both the year-to-date information and subtotals for each interim period. On September 25, 2018, the SEC issued guidance under a Compliance and Disclosure Interpretation ( C&DI 105.09 ) to clarify the effective date of the requirement. Under the guidance in C&DI 105.09, the Company plans to implement this updated disclosure requirement beginning with the first quarter 2019 Form 10-Q.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ( ASU 2018-07 ). ASU 2018-07 largely aligns the accounting for share-based payment awards issued to employees and nonemployees by expanding the scope of Topic 718 to apply to nonemployee share-based transactions, as long as the transaction is not effectively a form of financing. The new guidance will be effective for the Company on January 1, 2019. The Company is currently evaluating the potential impact that this guidance may have on its consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ( ASU 2016-02 ). The new standard requires that all lessees recognize the assets and liabilities that arise from leases on the balance sheet and disclose qualitative and quantitative information about its leasing arrangements. The new standard will be effective for the Company on January 1, 2019. In July 2018, the FASB issued ASU 2018-11, *Leases (Topic 842) Targeted Improvements*, which provides entities the option to not provide comparative period financial statements and instead apply the transition requirements as of the effective date of the new standard. The Company plans to adopt the new standard using the optional method under ASU 2018-11.

Pursuant to the guidance under ASU 2016-02, the Company plans to elect the optional package of practical expedients, which will allow the Company to not reassess: (i) whether expired or existing contracts contain leases;

(ii) lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The new standard also allows entities to make certain policy elections, some of which the Company also plans to elect, including: (i) a policy to not record short-term leases on the balance sheet and (ii) a policy to not separate lease and non-lease components for certain classes of underlying assets. The Company believes that the

**Table of Contents**

most significant effects of this standard relate to the recognition of right-of-use assets and corresponding liabilities on its consolidated balance sheet, primarily related to its existing office space in Newton, MA, and providing new disclosures with regards to the Company's leasing activities.

In July 2018, the FASB issued ASU No. 2018-09, *Codification Improvements* ( ASU 2018-09 ). This amendment makes changes to a variety of topics to clarify, correct errors in, or make minor improvements to the Accounting Standards Codification. The majority of the amendments in ASU 2018-09 will be effective for the Company in annual periods beginning after December 15, 2018. The Company does not expect the adoption of ASU 2018-09 to have a material impact on its consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement Disclosure Framework-Changes to the Disclosure Requirement for Fair Value Measurement* ( ASU 2018-13 ). The amendments in ASU 2018-13 modify the disclosure requirements on fair value measurements in ASC 820, Fair Value Measurement, based on the concepts in the FASB Concepts Statement, including the consideration of costs and benefits. The amendments under ASU 2018-13 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. The Company is currently evaluating the effects the adoption of ASU 2018-13 will have on its consolidated financial statements and related disclosures.

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

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808) Clarifying the Interaction between Topic 808 and Topic 606* ( ASU 2018-18 ). The amendments in ASU No. 2018-18 clarify that certain transactions between collaborative arrangement participants should be accounted for as revenue under ASC 606 when the collaborative arrangement participant is a customer in the context of a unit of account. The amendments under ASU 2018-18 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. The amendments in ASU 2018-18 should be applied retrospectively to the date of initial application of ASC 606. The Company plans to adopt this guidance effective January 1, 2019 using the modified retrospective approach. The Company does not expect the adoption of this standard to have an impact on the Company's consolidated financial statements.

**3. Property and Equipment, net**

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

|                               |                                     | December 31, |        |
|-------------------------------|-------------------------------------|--------------|--------|
|                               | Estimated Useful                    |              |        |
|                               | Life Years                          | 2018         | 2017   |
| Laboratory equipment          | 4                                   | \$ 593       | \$ 593 |
| Furniture and fixtures        | 5                                   | 607          | 381    |
| Office and computer equipment | 3                                   | 559          | 378    |
| Leasehold improvements        | Lesser of useful life or lease term | 5,397        | 3,391  |

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|  |          |          |
|--|----------|----------|
|  | 7,156    | 4,743    |
| Less accumulated depreciation and amortization | (3,293)  | (2,558)  |
|  | \$ 3,863 | \$ 2,185 |

Depreciation and amortization expense recorded for the years ended December 31, 2018, 2017, and 2016 was \$735, \$713 and \$717, respectively.



**Table of Contents****4. Investments**

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

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

The following table summarizes the Company's investments in debt securities, classified as available-for-sale as of December 31, 2017 (in thousands):

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

At December 31, 2018 and December 31, 2017, the Company held 79 and 54 debt securities, respectively, that were in an unrealized loss position. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2018 and 2017 was \$180,627 and \$96,623, respectively. As of December 31, 2018, 8 corporate debt securities with a fair value of \$14,882 had been in a continuous unrealized loss position for more than 12 months. The unrealized losses of \$47 related to these corporate debt securities are included in accumulated other comprehensive loss as of December 31, 2018. At December 31, 2018, the Company did not intend to sell the securities with an unrealized loss

position in accumulated other comprehensive income, and it is not likely that the Company will be required to sell these securities before recovery of their amortized cost basis. As of December 31, 2017, no securities had been in a continuous unrealized loss position for more than 12 months.

The Company reviews investments for other-than-temporary impairment whenever the fair value of an investment is less than the amortized cost and evidence indicates that an investment's carrying amount is not recoverable within a reasonable period of time. Other-than-temporary impairments of investments are recognized in the consolidated statements of operations if the Company has experienced a credit loss and has the intent to sell the investment or if it is more likely than not that the Company will be required to sell the investment before

**Table of Contents**

recovery of the amortized cost basis. Evidence considered in this assessment includes reasons for the impairment, compliance with the Company's investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period. The unrealized losses at December 31, 2018 and 2017 are attributable to changes in interest rates and the Company does not believe any unrealized losses represent other-than-temporary impairments.

**5. Accrued Expenses**

Accrued expenses consisted of the following (in thousands):

|                                    | <b>December 31,</b> |                  |
|------------------------------------|---------------------|------------------|
|                                    | <b>2018</b>         | <b>2017</b>      |
| Research and development costs     | \$ 15,903           | \$ 16,198        |
| Payroll and employee-related costs | 10,103              | 3,982            |
| Professional fees                  | 4,931               | 972              |
| Other                              | 1,556               | 293              |
|                                    | <b>\$ 32,493</b>    | <b>\$ 21,445</b> |

**6. Related Party Transactions**

The Company incurred expenses for consulting and contract research services with certain related parties, including a family member of management, a board member and a private diagnostics company, of which three members of the Company's Board of Directors, including the Company's CEO, were also members of the private company's Board of Directors. The Company paid consulting services of \$181 and \$101 for the years ended December 31, 2018 and 2017, respectively, and consulting and histopathology services of \$269 for the year ended December 31, 2016, to these related parties. At December 31, 2018 and 2017, there was \$0 and \$34, respectively, included in accounts payable and accrued expenses due to related parties.

**7. Stockholders' Equity*****Underwritten Offerings***

On May 7, 2018, the Company completed a follow-on offering under its shelf registration statement on Form S-3 (File No. 333-222726) pursuant to which the Company issued an aggregate of 10,525,424 shares of common stock, which included the full exercise of the underwriters' option to purchase additional shares, at a public offering price of \$14.75 per share. The Company received aggregate net proceeds of approximately \$145,720 from the offering after deducting the underwriting discounts and commissions and other offering expenses.

On April 28, 2017, the Company completed a follow-on offering under its shelf registration statement on Form S-3 (File No. 333-214489) pursuant to which the Company issued an aggregate of 3,902,439 shares of common stock at a public offering price of \$10.25 per share. The Company received net proceeds of approximately \$37,900 from the offering after deducting the underwriting discount and commissions and offering expenses.

***Controlled Equity Offering Sales Agreement***

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On December 7, 2015, the Company entered into a Controlled Equity Offering Sales Agreement (as amended on November 7, 2016 and December 1, 2017, the Sales Agreement ) with Cantor Fitzgerald & Co., as sales agent ( Cantor ), pursuant to which the Company issued and sold through Cantor an aggregate of 9,172,159 shares of the Company s common stock, for net proceeds of approximately \$89,053. The Sales Agreement was terminated effective August 12, 2018. Under the Sales Agreement, Cantor sold shares of the

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**Table of Contents**

Company's common stock by methods deemed to be an at-the-market offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (the Securities Act). The Company paid Cantor a commission of up to 3.0% of the gross proceeds from the sale of the shares of the Company's common stock pursuant to the Sales Agreement and provided Cantor with customary indemnification and contribution rights.

During the year ended December 31, 2018, the Company did not sell any shares under the Sales Agreement. During the years ended December 31, 2017 and 2016, the Company sold an aggregate of 3,405,763 shares and 5,645,082 shares, respectively, under the Sales Agreement for net proceeds of approximately \$36,978 and \$50,573, respectively.

***Open Market Sale Agreement***

On August 17, 2018, the Company entered into an Open Market Sale Agreement (the Open Market Sale Agreement) with Jefferies LLC, as agent (Jefferies), pursuant to which the Company may issue and sell shares of its common stock having an aggregate offering price of up to \$75,000 (the Open Market Shares) from time to time through Jefferies (the Open Market Offering).

Under the Open Market Sale Agreement, Jefferies may sell the Open Market Shares by methods deemed to be an at the market offering as defined in Rule 415(a)(4) promulgated under the Securities Act. The Company may sell the Open Market Shares in amounts and at times to be determined by the Company from time to time subject to the terms and conditions of the Open Market Sale Agreement, but it has no obligation to sell any of the Open Market Shares in the Open Market Offering.

The Company or Jefferies may suspend or terminate the offering of Open Market Shares upon notice to the other party and subject to other conditions. The Company has agreed to pay Jefferies commissions for its services in acting as agent in the sale of the Open Market Shares in the amount of up to 3.0% of gross proceeds from the sale of the Open Market Shares pursuant to the Open Market Sale Agreement. The Company has also agreed to provide Jefferies with customary indemnification and contribution rights.

The Company has not sold any shares to date under the Open Market Sale Agreement.

**8. Commitments and Contingencies**

***Operating Leases***

In 2014, the Company entered into an operating lease and subsequent amendments to lease approximately 46,167 square feet of office and research space in Newton, Massachusetts with a term through September 30, 2022. The lease provided the Company with an allowance for improvements of \$1,616 which was incurred in the first quarter of 2015. In February 2018, the lease was amended to extend the term of the lease to September 30, 2025 and expand the leased premises to approximately 62,143 square feet. In June 2018, the lease was further amended to expand the premise to a total of approximately 98,502 square feet with no change to the lease term. The 2018 lease amendments provided the Company with an allowance for improvements of \$2,131, which was fully incurred during the year ended December 31, 2018.

The Company evaluated the lease amendments and determined that the classification of the lease as an operating lease had not changed, and that the amendments did not constitute a new lease. As such, the unamortized balances of the existing deferred rent and tenant improvement allowances, along with the additions to deferred rent and tenant improvement allowances, are being amortized through September 30, 2025. All improvements were deemed normal tenant improvements, were recorded as leasehold improvements and deferred rent and are being recorded as a

reduction to rent expense ratably over the lease term. The Company is recording rent expense on a straight-line basis through the end of the lease term, inclusive of the period in which there are no scheduled rent payments. The Company has recorded deferred rent on the consolidated balance

**Table of Contents**

sheets at December 31, 2018 and December 31, 2017, accordingly. Finally, the Company has provided a security deposit in the form of a cash-collateralized letter of credit in the amount of \$550. The amount is classified within non-current restricted cash on the consolidated balance sheet.

The Company is also party to immaterial operating leases in both Munich, Germany and Tel Aviv, Israel with lease periods through January 2020 and June 2019, respectively. Monthly rent is approximately \$8 under the Munich, Germany lease and \$11 monthly under the Tel Aviv, Israel lease using December 31, 2018 exchange rates.

As of December 31, 2018, the minimum future rent payments under the lease agreements are as follows (in thousands):

|  |                  |
|--|------------------|
| 2019                                       | \$ 3,046         |
| 2020                                       | 3,208            |
| 2021                                       | 3,277            |
| 2022                                       | 3,447            |
| 2023                                       | 3,718            |
| Thereafter                                 | 6,735            |
| <b>Total future minimum lease payments</b> | <b>\$ 23,431</b> |

The Company recorded rent expense totaling \$2,480, \$1,198 and \$1,150 for the years ended December 31, 2018, 2017, and 2016, respectively.

***Research Agreements***

In July 2011 and September 2013, the Company entered into research agreements in which the Company received payments upon the achievement of certain milestones. The agreements require the Company to pay royalties on product sales and on a portion of any other sublicense income. The Company made payments of \$540 and \$2,221 in connection with these agreements in the years ended December 31, 2018 and 2017, respectively, and recorded these amounts to research and development expense. No royalty payments on product sales have been made to date.

***Litigation***

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

**9. Asset Purchase and License Agreements*****Antengene License Agreement***

Effective May 23, 2018 (the Antengene Effective Date), the Company entered into a License Agreement (Antengene License Agreement) with Antengene Therapeutics Limited, a corporation organized and existing under the laws of Hong Kong (Antengene) and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People's Republic of China, pursuant to which the Company granted Antengene exclusive rights to develop and commercialize, at its own cost, (i) selinexor, the Company's lead, novel, oral Selective Inhibitor of

Nuclear Export ( SINE ) compound, (ii) eltanexor, the Company's second-generation oral SINE compound, and (iii) KPT-9274, the Company's first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of PAK4 and NAMPT, each for the diagnosis, treatment and/or prevention of all human oncology indications (the Oncology Field ), as well as (iv) verdinexor, the Company's lead compound in development for the treatment of viral indications for the diagnosis, treatment and/



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**Table of Contents**

or prevention of certain human non-oncology indications (the Non-Oncology Field ) (the Antengene Licensed Compounds ). The Company licensed the development and commercial rights to Antengene for selinexor and eltanexor in the Oncology Field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the Oncology Field and verdinexor in the Non-Oncology Field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam (the Antengene Territory ).

Pursuant to the terms of the Antengene License Agreement, the Company received an upfront payment of \$11,703, and could receive up to \$105,000 in milestone payments if certain development goals are achieved and up to \$45,000 in milestone payments if certain sales milestones are achieved, as well as a high single-digit to low double-digit royalty based on future net sales of the Antengene Licensed Compounds in the Antengene Territory. In addition, upon Antengene's election and the parties' full execution of a manufacturing technology transfer plan and satisfaction of other specified conditions (the Antengene Manufacturing Election ), the Company will grant to Antengene non-exclusive rights to manufacture the Antengene Licensed Compounds and products containing such compounds in or outside of the Antengene Territory solely for development and commercialization in the fields in the Antengene Territory.

As part of the Antengene License Agreement, Antengene will also have the right to participate in global clinical studies of the Antengene Licensed Compounds and will bear the cost and expense for patients enrolled in clinical studies in the Antengene Territory. Antengene is responsible for seeking regulatory and marketing approvals for the Antengene Licensed Compounds in the Antengene Territory, as well as any development of the products specifically necessary to obtain such approvals. Antengene is also responsible for the commercialization of the Antengene Licensed Compounds in the Oncology Field and Non-Oncology Field, as applicable, in the Antengene Territory at its own cost and expense.

Until such time as Antengene elects to manufacture its own drug substance, the Company will furnish clinical supplies of drug substance to Antengene for use in Antengene's development efforts pursuant to a clinical supply agreement to be entered into by the Company and Antengene, and Antengene may elect to have the Company provide commercial supplies of drug product to Antengene pursuant to a commercial supply agreement to be entered into by the Company and Antengene, in each case the costs of which will be borne by Antengene.

The Antengene License Agreement will continue in effect on a product-by-product, country-by-country basis until the later of the tenth anniversary of the first commercial sale of the applicable product in such country or the expiration of specified patent protection and regulatory exclusivity periods for the applicable product in such country. However, the Antengene License Agreement may be terminated earlier by (i) either party for breach of the Antengene License Agreement by the other party or in the event of the insolvency or bankruptcy of the other party, (ii) Antengene on a product-by-product basis for certain safety reasons or on a product-by-product, country-by-country basis for any reason with 180 days' prior notice or (iii) the Company in the event Antengene challenges or assists with a challenge to certain of the Company's patent rights.

The Company assessed the Antengene arrangement in accordance with ASC 606 and concluded that the contract counterparty, Antengene, is a customer. The Company identified the following material promises under the contract: (i) exclusive licenses for each Antengene Licensed Compound, (ii) initial data transfers for each Antengene Licensed Compound, which consisted of regulatory data compiled by the Company for the Antengene Licensed Compounds as of the Antengene Effective Date, and (iii) obligations to stand-ready to provide an initial clinical supply for each Antengene Licensed Compound. The Company also identified immaterial promises under the contract relating to information exchanges and participation on operating committees and other working groups. Separately, the Company also identified certain customer options that would create an obligation for the Company if exercised by Antengene,

including (i) additional data transfers for each Antengene Licensed Compound, which would consist of the transfer of additional regulatory data compiled by the Company for each Antengene Licensed Compound after the Antengene Effective Date, (ii) obligations to provide

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**Table of Contents**

additional clinical supply and related substance supply for each Antengene Licensed Compound upon request by Antengene, (iii) manufacturing technology transfers and licenses for each Antengene Licensed Compound under the Antengene Manufacturing Election, as detailed above, and (iv) options for a backup compound, which represents Antengene's option to select a replacement compound in the event it elects to discontinue the development of the Antengene Licensed Compounds (the Antengene Transfer Options). The Antengene Transfer Options individually represent material rights, as they were offered at a significant and incremental discount. Therefore, they were further assessed as performance obligations under the Antengene License Agreement. Finally, the Company also identified certain other customer options that would create a manufacturing obligation for the Company if exercised by Antengene, including for commercial supply. These options do not represent a material right, as they are not offered at a significant and incremental discount.

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

The Company further determined that the up-front payment of \$11,703 constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on their relative stand-alone selling prices. The Company determined that substantially all of the total standalone selling price in the arrangement is derived from the four Antengene Combined License Obligations for selinexor, eltanexor, KPT-9274 and verdinexor. In connection therewith, the Company also estimated the standalone selling price for each of the material rights within the Antengene Transfer Options, and determined that such amounts were insignificant, and, therefore, immaterial for purposes of allocation. Accordingly, the Company allocated the \$11,703 transaction price amongst the Antengene Combined License Obligations as follows: \$9,363 for selinexor, \$1,053 for eltanexor, \$1,053 for KPT-9274, and \$234 for verdinexor. The Company believes that a change in the assumptions used to determine its best estimate of the stand-alone selling prices for any of the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

Upon execution of the Antengene License Agreement, the only fixed component of the transaction price included the \$11,703 up-front payment owed to the Company. As referenced above, the Company is eligible to receive additional payments of up to \$105,000 in milestone payments if certain development goals are achieved and up to \$45,000 in milestone payments if certain sales milestones are achieved, as well as a high single-digit to low double-digit royalty on future net sales of the Antengene Licensed Compounds in the Antengene Territory. In addition, the Company would receive cost reimbursement in connection with Antengene's election to receive additional clinical supply for the Antengene Licensed Compounds in the future. The future regulatory milestones and cost reimbursement for providing additional clinical supply of the Antengene Licensed Compounds, both of which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price at contract

inception and/or through December 31, 2018, because the amounts were fully constrained as of December 31, 2018. As part of its evaluation of the constraint, the Company

**Table of Contents**

considered numerous factors, including that receipt of such amounts is outside the control of the Company. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Antengene, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property licenses granted to Antengene and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as the Company's accounting policy. The Company will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

Through December 31, 2018, the Company has recognized no revenue under the Antengene License Agreement. Revenue will be recognized for (i) the Antengene Combined License Obligation for selinexor once the initial clinical supply of selinexor is delivered, which is currently expected to occur before March 31, 2019. Revenue will be recognized for (ii) the Antengene Combined License Obligation for eltanexor, (iii) the Antengene Combined License Obligation for KPT-9274, and (iv) the Antengene Combined License Obligation for verdinexor once the Company's completes both initial data transfer and the promise to stand-ready to provide initial clinical supply of the Antengene Licensed Compound in the future is fulfilled. The Company currently expects such promises will be fulfilled more than 12 months from the balance sheet date of December 31, 2018. Accordingly, and as of December 31, 2018, the entire \$11,703 upfront payment represents a contract liability, (i) \$9,363 of which was included in deferred revenue and is classified as a current liability in the consolidated balance sheet and (ii) \$2,340 of which was included in deferred revenue and is classified as a non-current liability in the consolidated balance sheet.

***Biogen Asset Purchase Agreement***

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

Under the terms of the APA and Letter Agreement, the Company sold to Biogen exclusive worldwide rights to develop and commercialize the Company's oral SINE compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis ("ALS") (the "Transfer of IP"), and also granted Biogen: (i) an exclusive worldwide license under certain of the Company's intellectual property to manufacture or have manufactured KPT-350 (the "Manufacturing License"), (ii) a technology transfer package, consisting of information and the Company's know-how regarding the manufacture of KPT-350 (the "Manufacturing Technology Transfer"), (iii) a right, at Biogen's request, to have the Company provide transition assistance regarding manufacturing and other matters (the "Transition Assistance"), (iv) existing inventory of KPT-350 (the "Inventory"), (v) an initial supply of KPT-350 (the "Initial Supply"), and (vi) a right, at Biogen's request, to have the Company manufacture and supply the active pharmaceutical ingredient for an additional supply of KPT-350 (the "Additional Supply"). In consideration for these rights, the Company received an upfront payment of \$10,000, and is eligible to receive additional payments of up to \$142,000 based on the achievement by Biogen of future specified development milestones, and up to \$65,000 based on the achievement by Biogen of future specified commercial milestones. The Company will also be eligible to receive tiered royalty payments that reach low double-digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product and the expiration of specified patent protection for the applicable product, determined on a country-by-country basis.

The Company and Biogen have made customary representations and warranties and agreed to customary covenants in the APA, including covenants requiring Biogen to use commercially reasonable efforts to develop KPT-350 in specified neurological indications, including ALS, in any of the United States, United Kingdom, France, Spain, Germany or Italy. The APA will continue in effect until the expiration of all royalty obligations, provided that the APA may be terminated earlier by Biogen, subject to the requirements that Biogen (i) negotiate in good faith with the Company regarding an assignment or license back to the Company of the purchased assets and (ii) not transfer or

license the purchased assets to a third party unless such third party assumes Biogen's obligations to the Company under the APA.

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**Table of Contents**

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Biogen, is a customer. The Company identified the following material promises in the arrangement: the Transfer of IP and the Manufacturing License. The Company also identified immaterial promises under the contract that were not deemed performance obligations. The Company further determined that other promises for Additional Supply and Transition Assistance represented customer options, which would create an obligation for the Company if exercised by Biogen. Since no additional or material consideration is owed to the Company by Biogen upon exercise of the customer options for Additional Supply and Transition Assistance, the Company determined that both are offered at significant and incremental discounts. Accordingly, they were assessed as material rights and, therefore, separate performance obligations in the arrangement. The Company then determined that the Transfer of IP and the Manufacturing License were not distinct from one another and must be combined as a performance obligation (the Combined Performance Obligation ). This is because Biogen requires the Manufacturing License to derive benefit from the Transfer of IP. Based on these determinations, as well as the considerations noted above with respect to the material rights for Additional Supply and Transition Assistance, the Company identified three distinct performance obligations at the inception of the contract: (i) the Combined Performance Obligation, (ii) the material right for Additional Supply, and (iii) the material right for Transition Assistance.

The Company further determined that the up-front payment of \$10,000 constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on their relative stand-alone selling prices. In connection therewith, the Company estimated the stand-alone selling price of the (i) Combined Performance Obligation, (ii) material right for Additional Supply, and (iii) material right for Transition Assistance, and determined that the stand-alone selling price of the material rights for Additional Supply and Transition Assistance were insignificant based on various quantitative and qualitative considerations. Accordingly, the Company further determined that the allocation of the transaction price to the material rights for Additional Supply and Transition Assistance was insignificant. Based on the estimates of the stand-alone selling prices for each of the performance obligations, the Company determined that substantially all the \$10,000 transaction price should be allocated to the Combined Performance Obligation. The Company believes that a change in the assumptions used to determine its best estimate of the stand-alone selling prices for the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

Upon execution of the APA, the transaction price included only the \$10,000 up-front payment owed to the Company. The Company may receive further payments upon the achievement of certain regulatory and sales milestones, as detailed above, as well as tiered royalty payments that reach low double-digits based on future net sales. The future regulatory milestones, which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price, because the amounts were fully constrained as of December 31, 2018. As part of its evaluation of the constraint, the Company considered numerous factors, including that receipt of such milestones is outside the control of the Company. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Biogen, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as the Company's accounting policy. The Company will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

During the year ended December 31, 2018, the Company recognized \$10,000 of revenue, as it had satisfied its promises under the Combined Performance Obligation by transferring the underlying promised goods during the first quarter of 2018.

***Ono License Agreement***

Effective October 11, 2017 (the Ono Effective Date ), the Company entered into a license agreement (the Ono License Agreement ) with Ono Pharmaceutical Co., Ltd., a corporation organized and existing under the



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**Table of Contents**

laws of Japan ( Ono ), pursuant to which the Company granted Ono exclusive rights to develop and commercialize, at its own cost, selinexor and eltanexor, for the diagnosis, treatment and/or prevention of all human oncology indications (the Ono Field ) in Japan, Republic of Korea, Republic of China (Taiwan) and Hong Kong, as well as in the ten Southeast Asian countries currently comprising the Association of Southeast Asian Nations (the Ono Territory ) (the Ono Exclusive License ). Pursuant to the terms of the Ono License Agreement, the Company received an upfront payment of ¥2.5 billion (US\$21,916 on the date received), and could receive up to ¥10.15 billion (approximately US\$90,500 at the exchange rate as of the Ono Effective Date) in milestone payments if certain development goals are achieved and up to ¥9.0 billion (approximately US\$80,200 at the exchange rate as of the Ono Effective Date) in milestone payments if certain sales milestones are achieved, as well as a low double-digit royalty based on future net sales of selinexor and eltanexor in the Ono Territory. In addition, upon Ono s election and the parties full execution of a manufacturing technology transfer plan and satisfaction of other specified conditions (the Ono Manufacturing Election ), the Company will grant to Ono non-exclusive rights to manufacture selinexor, eltanexor and products containing such compounds in or outside of the Ono Territory solely for development and commercialization in the Ono Field in the Ono Territory.

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

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

The Ono License Agreement will continue in effect on a product-by-product, country-by-country basis until the later of the tenth anniversary of the first commercial sale of the applicable product in such country or the expiration of specified patent protection and regulatory exclusivity periods for the applicable product in such country. However, the Ono License Agreement may be terminated earlier by (i) either party for breach of the Ono License Agreement by the other party or in the event of the insolvency or bankruptcy of the other party, (ii) Ono on a product-by-product basis for certain safety reasons or on a product-by-product, country-by-country basis for any reason with 180 days prior notice or (iii) the Company in the event Ono challenges or assists with a challenge to certain of the Company s patent rights.

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Ono, is a customer. The Company identified the following material promises under the contract: (i) the Ono Exclusive License for selinexor and eltanexor, (ii) initial data transfer for selinexor and eltanexor, which consisted of regulatory data compiled by the Company for the licensed compounds and products as of the Ono Effective Date, (iii) initial clinical supply for selinexor, which consisted of units of clinical supply for Ono to conduct its Phase I Trial, and (iv) an obligation to stand-ready to provide initial clinical supply for eltanexor. The Company also identified immaterial promises under the contract relating to information exchanges, and participation on operating committees and other working groups. Separately, the Company also identified certain customer options that would create an obligation for the Company if exercised by Ono, including the (i) additional data transfer for selinexor and eltanexor, which would consist of the transfer of additional regulatory data compiled by the Company for the licensed compounds and products after the Ono Effective Date, (ii) additional clinical supply and related substance supply for

selinexor and eltanexor, which would consist of supplying Ono with units and substance of selinexor and eltanexor incremental to the initial clinical supply for selinexor and the obligation to stand-ready to provide initial clinical supply for eltanexor, as noted above, (iii) manufacturing technology transfer and license for selinexor and eltanexor under the Ono Manufacturing

**Table of Contents**

Election, as detailed above, and (iv) options for a backup compound, which represents Ono's option to select a replacement compound in the event it elects to discontinue the development of either of the licensed compounds (the Ono Transfer Options). The Ono Transfer Options individually represent material rights, as they were offered at a significant and incremental discount. Therefore, they were further assessed as performance obligations under the Ono License Agreement. The Company also identified certain other customer options that would create a manufacturing obligation for the Company if exercised by Ono, including commercial supply. This option is referred to herein as the Ono Manufacturing Option. The Ono Manufacturing Option does not represent a material right, as it is not offered at a significant and incremental discount.

In further evaluating the promises detailed above, the Company determined that the (i) Ono Exclusive License, initial data transfer, and initial clinical supply for selinexor and (ii) Ono Exclusive License, initial data transfer, and obligation to stand-ready to provide initial clinical supply of eltanexor were not distinct from one another, and must be combined as two separate performance obligations (the Ono Combined License Obligation for selinexor and the Ono Combined License Obligation for eltanexor). This is because, for both selinexor and eltanexor, Ono requires the initial data transfer and clinical supply to derive benefit from the Ono Exclusive License since the Company did not grant manufacturing licenses for selinexor and eltanexor at contract inception. The Company also determined that each of the Ono Transfer Options represents a distinct performance obligation. Based on these determinations, the Company identified six distinct performance obligations at the inception of the Ono License Agreement, including (i) the Ono Combined License Obligation for selinexor, (ii) the Ono Combined License Obligation for eltanexor, and the four components of the Ono Transfer Options, including (iii) the material right for additional data transfer, (iv) the material right for additional clinical supply and related substance supply, (v) the material right for manufacturing technology transfer and license, and (vi) the material right for the option for a backup compound.

The Company further determined that the up-front payment of ¥2.5 billion (US\$21,916 on the date received) constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on the Company's best estimate of their relative stand-alone selling prices. The Company determined that substantially all of the total standalone selling price in the arrangement is derived from the Ono Combined License Obligation for selinexor and the Ono Combined License Obligation for eltanexor. In connection therewith, the Company estimated the standalone selling price for each of the material rights within the Ono Transfer Options, and determined that such amounts were insignificant, and, therefore, immaterial for purposes of allocation. Accordingly, the Company allocated the ¥2.5 billion (US\$21,916 on the date received) upfront transaction price between the Ono Combined License Obligations as follows: \$19,724 for selinexor and \$2,192 for eltanexor. The Company believes that a change in the assumptions used to determine its best estimate of the stand-alone selling prices for any of the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

Upon execution of the Ono License Agreement, the transaction price included only the ¥2.5 billion (US\$21,916 on the date received) up-front payment owed to the Company. As referenced above, the Company is eligible to receive additional payments of up to ¥10.15 billion based on the achievement by Ono of future specified development milestones and up to ¥9.0 billion based on the achievement by Ono of future specified commercial milestones, as well as a low double-digit royalty based on future net sales of selinexor and eltanexor in the Ono Territory. In addition, the Company could receive cost reimbursement in connection with its promise to stand-ready to provide initial clinical supply for eltanexor in the future. The future regulatory milestones and cost reimbursement for providing initial clinical supply of eltanexor, both of which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price, because the amounts were fully constrained as of December 31, 2018. As part of its evaluation of the constraint, the Company considered numerous factors, including that receipt of such amounts is outside the control of the Company. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Ono, will be recognized when the

related sales occur, as they were determined to relate predominantly to the intellectual property granted to Ono and, therefore, have also been

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**Table of Contents**

excluded from the transaction price in accordance with the sales-based royalty exception, as well as the Company's accounting policy. The Company will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

As the initial clinical supply of selinexor was delivered in April 2018, the Ono Combined License Obligation for selinexor was determined to be fulfilled and revenue of \$19,724 was recognized during the quarter ended June 30, 2018. The transaction price allocated to the Ono Combined License Obligation for eltanexor will be recognized as revenue once the Company's stand-ready promise to provide initial clinical supply of eltanexor in the future is fulfilled, which is the last remaining undelivered promise associated with the Ono Combined License Obligation for eltanexor. As of December 31, 2018, \$2,192 of the Ono License Agreement upfront payment is included in deferred revenue and is classified as a non-current liability in the consolidated balance sheet.

Given the determination that the license rights conveyed to Ono lacked standalone value from the initial clinical supply of product required for Ono to obtain benefit from the rights granted and the fact that no initial clinical supply had been provided to Ono as of December 31, 2017, the Company concluded that no revenue should be recognized under ASC 605. Arrangement consideration at the inception of the arrangement included the ¥2.5 billion (US\$21,916 on the date received) upfront payment. All other forms of consideration such as milestones and royalties, were considered contingent consideration, with no amount allocable to deliverables at the inception of the arrangement. The Company concluded that the contingent consideration would be recognized when the underlying contingencies have been resolved, assuming all other revenue recognition criteria are met. As the accounting treatment for this agreement did not materially differ under ASC 605 and ASC 606, and no revenue was recognized under the Company's previous accounting policy through December 31, 2017, no transition adjustment was recorded to the opening balance of accumulated deficit as of January 1, 2018. Accordingly, the upfront payment of ¥2.5 billion (US\$21,916 on the date received), which represents a contract liability, was also included in deferred revenue as of December 31, 2017.

***MMRF Research Agreement***

The Company is a party to a research agreement with the Multiple Myeloma Research Foundation (MMRF). Under this research agreement, the Company is obligated to make certain payments to MMRF, including if the Company out-licenses selinexor. The terms of this research agreement do not apply to eltanexor, KPT-9274 or verdinexor. During the year ended December 31, 2018, the Company paid approximately \$278 to MMRF, which reflects the amount owed to MMRF under the Antengene License Agreement transaction. In connection with the transaction pursuant to the Ono License Agreement, the Company paid to MMRF \$1,972 of the upfront cash payment from Ono in the year ended December 31, 2017. The Company will be obligated to pay a percentage of any milestone payments from Antengene and Ono and a mid-single-digit percentage of any royalty payments from Antengene and Ono. Such payments are recorded within research and development expense in the Company's consolidated statement of operations. As of December 31, 2018, a maximum of \$3,750 in potential future obligations to MMRF are remaining under the MMRF research agreement.

***Anivive License Agreement***

On April 28, 2017 (the Anivive Effective Date), the Company entered into a license agreement (the Anivive Agreement) with Anivive Lifesciences, Inc. (Anivive), a biopharmaceutical company engaged in the research, development and commercialization of animal health medicines, pursuant to which the Company has granted Anivive an exclusive, worldwide license to develop and commercialize verdinexor (KPT-335) for the treatment of cancer in companion animals (the Anivive Exclusive License). Pursuant to the terms of the Anivive Agreement, the Company received an upfront payment of \$1,000 and a payment of \$250 upon the completion of the technology transfer, which occurred during the year ended December 31, 2017. In addition, the Company is eligible to receive potential clinical,

regulatory and commercial development milestone payments totaling up to \$43,250, as well as a low double-digit royalty based on Anivive's future net sales of verdinexor

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**Table of Contents**

following commercialization. The potential future milestone payments are composed of \$5,750 based on achievement of clinical and regulatory milestone events and \$37,500 based on achievement of sales milestone events.

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Anivive, is a customer. The Company identified the following material promises under the contract, the Anivive Exclusive License and the technology transfer, which consisted of regulatory data compiled by the Company for the licensed compound and product as of the Anivive Effective Date. The Company also identified immaterial promises under the contract that were not deemed performance obligations, including participating on a product advisory committee and sharing regulatory matter information. The Company further determined that other promises for (i) transfer of additional technology in the future, if developed by the Company, and (ii) facilitating manufacturing and supply relationships with the Company's third-party contract manufacturers represented customer options, would create an obligation for the Company if exercised by Anivive. Since no additional or immaterial consideration is owed to the Company by Anivive upon exercise of the customer options noted, the Company determined that both are offered at significant and incremental discounts. Accordingly, they were assessed as material rights and, therefore, separate performance obligations in the arrangement.

In further evaluating the promises detailed above, the Company determined that the Anivive Exclusive License and the technology transfer were not distinct from one another and must be combined as a performance obligation (the Anivive Combined License Obligation). This is because Anivive requires the technology transfer to derive benefit from the Anivive Exclusive License. Based on these determinations, the Company identified three distinct performance obligations at the inception of the contract: (i) the Anivive Combined License Obligation, (ii) the material right for transfer of additional technology in the future, if developed by the Company, and (iii) the material right for facilitating manufacturing and supply relationships with the Company's third-party contract manufacturers.

The Company further determined that the up-front payment of \$1,000 upon contract execution, as well as the \$250 upon completion of the technology transfer, constituted the entirety of the consideration included in the transaction price as of the transition date, January 1, 2018, which was allocated to the performance obligations based on their relative stand-alone selling prices. In connection therewith, the Company estimated the stand-alone selling price of the (i) Anivive Combined License Obligation, (ii) material right for transfer of additional technology in the future, if developed by the Company, and (iii) the material right for facilitating manufacturing and supply relationships with the Company's third-party contract manufacturers, and determined that the stand-alone selling price of the material rights noted were insignificant based on various qualitative considerations. Accordingly, the Company further determined that the allocation of the upfront payment to the material rights noted was insignificant. Based on the estimates of the stand-alone selling prices for each of the performance obligations, the Company determined that substantially all the \$1,250 transaction price should be allocated to the Anivive Combined License Obligation. The Company believes that a change in the assumptions used to determine its best estimate of the stand-alone selling prices for the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

As referenced above, the up-front payment of \$1,000 upon contract execution, as well as the \$250 upon completion of the technology transfer, constituted the entirety of the consideration included in the transaction price as of the transition date, January 1, 2018. The Company is also eligible to receive additional payments up to \$5,750 based on achievement of clinical and regulatory milestone events and up to \$37,500 based on achievement of sales milestone events, as well as a low double-digit royalty based on Anivive's future net sales of verdinexor following commercialization. The future regulatory milestones, which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price, because the amounts were fully constrained as of December 31, 2018. As part of its evaluation of the constraint, the Company considered numerous factors, including that receipt of such milestones is outside the control of the Company. Separately, any consideration

related to sales-based milestones, as well as royalties on



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**Table of Contents**

net sales upon commercialization by Anivive, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property granted to Anivive and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as the Company's policy. The Company will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

To date, the Company recognized \$1,250 of revenue associated with the Anivive Agreement. Revenue for the upfront payment and technology transfer milestone was recognized upon completion of the technology transfer in October 2017, as all promises under the Anivive Combined License Obligation had been fulfilled.

The Company reached similar conclusions when evaluating this agreement under its previous accounting policy, which was based on legacy guidance within ASC 605. When evaluating this agreement under ASC 605, the Company concluded that the licenses to verdinexor and technology transfer concerning the licensed product are essential to Anivive's intended use of the license to develop and commercialize the licensed compound and represented a single unit of accounting. Other potential contractual obligations were evaluated and determined not to be deliverables at inception of the arrangement or were evaluated and determined to be immaterial to the arrangement and, therefore, not evaluated further in the Company's analysis. Arrangement consideration at the inception of the arrangement included the \$1,250 in upfront payments, which includes the milestone fee upon completion of the technology transfer. All other forms of consideration, such as milestones and royalties, were considered contingent consideration, with no amount allocable to deliverables at the inception of the arrangement. The Company concluded that the contingent consideration would be recognized when the underlying contingencies have been resolved, assuming all other revenue recognition criteria are met. Given the single unit of accounting and that the technology transfer would be the last item to be delivered within the unit of accounting, the Company concluded that revenue would be recognized upon the completion of delivery of the technology transfer assuming all other general revenue recognition criteria would be met as of that date. As the accounting treatment for this agreement did not materially differ under ASC 605 and ASC 606, and the upfront payment and technology transfer fee, totaling \$1,250, was recognized as revenue during the year ended December 31, 2017 in accordance with the Company's previous accounting policy, and would have also been recognized during the year ended December 31, 2017 in accordance with the Company's accounting policy under ASC 606, no transition adjustment was recorded to the opening balance of accumulated deficit as of January 1, 2018.

**10. Stock-based Compensation**

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

In October 2013, the Company's board of directors adopted and the Company's stockholders approved the 2013 Stock Incentive Plan (the 2013 Plan). The 2013 Plan became effective immediately prior to the closing of the IPO and provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other stock-based awards. The number of shares of common stock reserved for issuance under the 2013 Plan is equal to the sum of (1) 969,696 shares plus (2) the number of shares (up to 2,126,377 shares) equal to the sum of the number of shares of common stock then available for issuance under the 2010 Plan and the number of shares of common stock subject to outstanding awards under the 2010 Plan that expire,

terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right plus (3) an

**Table of Contents**

annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until, and including, the fiscal year ending December 31, 2023, equal to the lesser of (A) 1,939,393 shares of common stock, (B) 4% of the number of shares of common stock outstanding on the first day of such fiscal year, or (C) an amount determined by the Board.

In January 2016, 2017 and 2018, the number of shares available for issuance under the 2013 Plan was increased by 1,434,490, 1,675,513 and 1,939,393 shares of common stock, respectively. As of December 31, 2018, the Company had 1,866,696 shares available for issuance under the 2013 Plan.

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

|                            | <b>Year Ended December 31,</b> |                  |                  |
|----------------------------|--------------------------------|------------------|------------------|
|                            | <b>2018</b>                    | <b>2017</b>      | <b>2016</b>      |
| Research and development   | \$ 8,686                       | \$ 11,208        | \$ 12,142        |
| General and administrative | 8,589                          | 9,197            | 10,141           |
| <b>Total</b>               | <b>\$ 17,275</b>               | <b>\$ 20,405</b> | <b>\$ 22,283</b> |

**Stock Options**

Total expense related to employee and non-employee stock options for the years ended December 31, 2018, 2017 and 2016 was \$16,449, \$16,739 and \$17,867, respectively.

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

|  | <b>Shares</b> | <b>Weighted-<br/>Average<br/>Exercise<br/>Price</b> | <b>Weighted-<br/>Average<br/>Remaining<br/>Contractual<br/>Term (year)</b> | <b>Aggregate<br/>Intrinsic<br/>Value</b> |
|--|---------------|---|--|--|
| Options outstanding at December 31, 2017 | 7,019,083     | \$ 13.77  | 7.4  | \$ 11,897                                |
| Granted                                  | 3,627,100     | 12.80   |  |  |
| Exercised                                | (559,830)     | 4.73  |  |  |
| Forfeited                                | (1,169,269)   | 14.98   |  |  |
| Options outstanding at December 31, 2018 | 8,917,084     | \$ 13.78  | 7.4  | \$ 8,197                                 |
| Options exercisable at December 31, 2018 | 4,434,871     | \$ 15.61  | 6.0  | \$ 7,594                                 |

The total intrinsic value of stock options exercised for the years ended December 31, 2018, 2017 and 2016 was \$6,042, \$446 and \$347, respectively.

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

|                          | <b>Years Ended December 31,</b> |             |             |
|--------------------------|---------------------------------|-------------|-------------|
|                          | <b>2018</b>                     | <b>2017</b> | <b>2016</b> |
| Volatility               | 79%-81%                         | 79%-85%     | 79%-85%     |
| Expected term (in years) | 5.5-9.8                         | 5.5-9.6     | 5.5-9.8     |
| Risk-free interest rate  | 2.50%-3.05%                     | 1.76%-2.29% | 1.07%-2.09% |
| Dividend                 | %                               | %           | %           |

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**Table of Contents**

The Company uses the simplified method as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term for options granted to employees and utilizes the contractual term for options granted to non-employees. The expected term is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including early stage of product development and therapeutic focus. For these analyses, the Company selects companies with comparable characteristics to theirs including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the options. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The Company accounts for forfeitures as they occur. Through December 31, 2016, management estimated expected forfeitures based on historical data from the Company and recognized compensation costs only for those equity awards expected to vest.

Using the Black-Scholes option-pricing model, the weighted-average grant date fair values of options granted during the years ended December 31, 2018, 2017 and 2016 was \$8.91, \$7.22 and \$5.00 per share, respectively.

At December 31, 2018, the total unrecognized compensation related to unvested employee and non-employee stock option awards granted under the 2013 Plan was \$31,830, which the Company expects to recognize over a weighted-average period of approximately 2.8 years.

***Restricted Stock***

To date, the Company has granted 1,958,210 shares of restricted stock outside of the 2010 Plan and the 2013 Plan and 45,454 shares of restricted stock under the 2010 Plan. There was no expense related to employee and non-employee restricted stock for the years ended December 31, 2018, 2017 and 2016.

As of December 31, 2018, there was no unrecognized compensation cost related to employee and non-employee unvested restricted stock.

***Restricted Stock Units***

A restricted stock unit ( RSU ) represents the right to receive one share of the Company's common stock upon vesting of the RSU. The fair value of each RSU is based on the closing price of the Company's common stock on the date of grant. The Company grants RSUs with service conditions that vest in two equal annual installments provided that the employee remains employed with the Company ( Time-Based RSUs ). During the year ended December 31, 2017, the Company also granted performance-based RSUs, which vest upon the achievement of certain performance goals subject to the employee's continued employment ( Performance-Based RSUs ).

During the year ended December 31, 2018, the Company recognized \$180 of stock-based compensation expense related to a portion of the Performance-Based RSUs when the associated performance goal became probable of achievement in the first quarter and was achieved in the second quarter. The remaining 98,800 Performance-Based RSUs were forfeited in July 2018 when the performance goal was not achieved.

**Table of Contents**

During the year ended December 31, 2018, the Company granted 10,000 shares of RSUs under the 2013 Plan. The following is a summary of RSU activity for the 2013 Plan for the years ended December 31, 2018 and 2017, respectively:

|                               | <b>Number of<br/>Shares<br/>Underlying RSUs</b> | <b>Weighted-Average<br/>Grant Date<br/>Fair Value</b> |
|-------------------------------|---|---|
| Unvested at December 31, 2017 | 253,100   | \$ 10.27  |
| Granted                       | 10,000  | 8.90  |
| Forfeited                     | (124,300)                                       | 10.24   |
| Vested                        | (113,800)                                       | 10.26   |
| Unvested at December 31, 2018 | 25,000  | \$ 9.87   |

The total stock-based compensation expense related to RSUs, including Performance-Based RSUs, for the years ended December 31, 2018, 2017 and 2016 was \$377, \$3,447 and \$4,212, respectively.

As of December 31, 2018, there was \$182 of unrecognized compensation costs related to unvested Time-Based RSUs, which are expected to be recognized over a weighted average period of 1.9 years.

**Employee Stock Purchase Plan**

The Company has an Employee Stock Purchase Plan ( ESPP ) that permits eligible employees to enroll in six-month offering periods. Participants may purchase shares of the Company's common stock, through payroll deductions, at a price equal to 85% of the fair market value of the common stock on the first or last day of the applicable six-month offering period, whichever is lower. Purchase dates under the ESPP occur on or about May 1 and November 1 each year. In 2013, the Company's shareholders approved an increase in the number of shares of common stock authorized for issuance pursuant to the ESPP to 242,424 shares of common stock, plus an annual increase to be added on the first day of each fiscal year, commencing on January 1, 2015 and ending on December 31, 2023, equal to the lesser of 484,848 shares of the Company's common stock, 1% of the number of outstanding shares on such date, or an amount determined by the board of directors.

During the years ended December 31, 2018, 2017 and 2016, \$878, \$404 and \$340, respectively, was withheld from employees, on an after-tax basis, in order to purchase 98,770, 57,582 and 46,815 shares of the Company's common stock, respectively. For the years ended December 31, 2018, 2017 and 2016, the Company recorded stock-based compensation expense of \$449, \$219 and \$204, respectively. As of December 31, 2018, 334,741 shares of Company's common stock remained available for issuance under the ESPP. As of December 31, 2018, there was \$255 of total unrecognized stock-based compensation expense related to the ESPP. The expense is expected to be recognized over a period of four months.

The fair value of the option component of the shares purchased under the ESPP was estimated using the Black-Scholes option-pricing model with the following weighted-average assumptions:

|                          | <b>Years Ended<br/>December 31,</b> |             |
|--------------------------|-------------------------------------|-------------|
|                          | <b>2018</b>                         | <b>2017</b> |
| Volatility               | 48.2%-61.2%                         | 48.2%-77.8% |
| Expected term (in years) | 0.5                                 | 0.5         |
| Risk-free interest rate  | 1.30%-2.05%                         | 0.5%-1.30%  |
| Dividend                 | %                                   | %           |

**11. 401(k) Plan**

The Company has a 401(k) retirement and profit-sharing plan (the "401(k) Plan") covering all qualified employees. The 401(k) Plan allows each participant to contribute a portion of their base wages up to an amount

**Table of Contents**

not to exceed an annual statutory maximum. Effective January 1, 2011, the Company adopted a Safe Harbor Plan that provides a Company match up to 4% of salary. The Company contributed a match of \$1,121, \$572 and \$491 to the 401(k) Plan for the years ended December 31, 2018, 2017 and 2016, respectively.

**12. Income Taxes*****New Tax Legislation***

On December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act ( TCJA ). This legislation reduced the U.S. corporate tax rate from the current rate of 34% to 21% for tax years beginning after December 31, 2017. As a result of the enacted law, the Company was required to revalue deferred tax assets and liabilities existing as of December 31, 2017 from the 34% federal rate in effect through the end of 2017, to the new 21% rate. The Company has recognized the impact of the TCJA in these consolidated financial statements and related disclosures. Due to the complexities involved in accounting for the enactment of the TCJA, the SEC staff issued Staff Accounting Bulletin No. 118 ( SAB 118 ), which allows a registrant to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. In accordance with SAB 118, the Company recorded provisional amounts reflecting the impact of the TCJA in these consolidated financial statements and related disclosures. In the current year the Company recorded an impact of \$(464) related to the return to provision items for federal rate change, which is offset by a full valuation allowance. The impact of the remeasurement of the Company's U.S. deferred tax assets and liabilities to 21% resulted in the reduction of deferred tax assets of approximately \$42,763, which is offset by a full valuation allowance. There was no impact to the Company's income statement due to the reduction in the U.S. corporate tax rate. The Company has finalized its analysis of the impact of the TCJA and noted there were no material changes from its initial assessment.

***Income Taxes***

For the year ended December 31, 2018, 2017 and 2016, the Company recorded an income tax expense of \$26, \$63 and \$139 for its operations in Germany. The Company's foreign tax provision pertains to foreign income taxes due at its German subsidiary which operates on a cost plus profit margin.

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

|               | <b>Year Ended<br/>December 31,</b> |                     |                     |
|---------------|------------------------------------|---------------------|---------------------|
|               | <b>2018</b>                        | <b>2017</b>         | <b>2016</b>         |
| Foreign       | \$ (28,689)                        | \$ (35,680)         | \$ (26,928)         |
| U.S.          | (149,692)                          | (93,241)            | (82,510)            |
| <b>Totals</b> | <b>\$ (178,381)</b>                | <b>\$ (128,921)</b> | <b>\$ (109,438)</b> |



**Table of Contents**

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following:

|   | <b>Year Ended<br/>December 31,</b> |             |
|---|------------------------------------|-------------|
|   | <b>2018</b>                        | <b>2017</b> |
| <b>Deferred tax assets:</b>                     |                                    |             |
| U.S. and state net operating loss carryforwards | \$ 116,236                         | \$ 84,556   |
| Stock-based compensation                        | 11,228                             | 15,748      |
| Accruals and other temporary differences        | 3,605                              | 2,386       |
| Research and development credits                | 49,307                             | 29,186      |
| Capitalized research and development            | 1,388                              | 2,211       |
| Fixed Assets and Intangibles                    | 6,422                              |             |
| Deferred Revenue                                | 527                                |             |
| Foreign net operating loss carryforwards        | 72                                 |             |
| Valuation allowance                             | (173,247)                          | (134,087)   |
| <b>Total deferred tax assets</b>                | <b>15,538</b>                      |             |
| <b>Deferred tax liabilities:</b>                |                                    |             |
| Convertible debt amortization                   | (15,538)                           |             |
| <b>Total deferred tax liabilities</b>           | <b>(15,538)</b>                    |             |
| <b>Net deferred tax assets</b>                  | <b>\$</b>                          | <b>\$</b>   |

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2018 and 2017. The valuation allowance increased approximately \$39,160 during the year ended December 31, 2018 due primarily to the generation of net operating losses and increased approximately \$3,766 for tax year ended December 31, 2017 due primarily to the generation of net operating losses, offset by the revaluation of the deferred assets at a 21% Federal tax rate.

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes as reflected in the financial statements is as follows:

|  | <b>Year Ended<br/>December 31,</b> |             |             |
|--|------------------------------------|-------------|-------------|
|  | <b>2018</b>                        | <b>2017</b> | <b>2016</b> |
| Federal income tax expense at statutory rate | 21.0%                              | 34.0%       | 34.0%       |
| State income tax, net of federal benefit     | 0.7%                               | 5.9%        | 3.3%        |
| Permanent differences                        | %                                  | (3.9)%      | (3.1)%      |

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|                                 |         |         |         |
|---------------------------------|---------|---------|---------|
| Research and development credit | 7.8%    | 8.4%    | 4.8%    |
| Foreign rate differential       | (3.4)%  | (9.4)%  | (8.5)%  |
| Change in valuation allowance   | (28.2)% | (1.4)%  | (25.1)% |
| Provision to return adjustments | 2.4%    | 1.0%    | (5.5)%  |
| Other                           | (0.6)%  | (1.4)%  | %       |
| Federal rate change             | 0.3%    | (33.2)% | %       |
| Effective income tax rate       | %       | %       | (0.1)%  |

As of December 31, 2018 and 2017, the Company had U.S. federal net operating loss carryforwards of approximately \$426,954 and \$300,843, respectively, which may be able to offset future income tax liabilities. Of the \$426,954 carryforward as of December 31, 2018, \$134,087 of the carryforward has an indefinite life and \$292,867 will expire at various dates through 2037. As of December 31, 2018 and 2017, the Company had U.S. state net operating loss carryforwards of approximately \$414,818 and \$332,330, respectively, which may be

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**Table of Contents**

available to offset future state income tax liabilities and expire at various dates through 2038. Also as of December 31, 2018, the Company had foreign net operating loss carryforwards of approximately \$311, which may be able to offset future foreign income tax liabilities. The foreign net operating loss stems from the Company's Israel subsidiary and the loss has an indefinite life.

As of December 31, 2018 and 2017, the Company had federal research and development tax credit carryforwards of approximately \$46,944 and \$27,384, respectively, available to reduce future tax liabilities, which expire at various dates through 2038. As of December 31, 2018 and 2017, the Company had state research and development tax credit carryforwards of approximately \$2,991 and \$2,282, respectively, available to reduce future tax liabilities, which expire at various dates through 2033. The Company completed a study of its R&D tax credits through December 31, 2017 and adjusted its deferred tax asset for the result of that study. For the year ending December 31, 2018, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. Previously, the Company has completed several financings since its inception, which resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code. The Company completed a Section 382 analysis through July 31, 2015 and subsequently reduced its deferred tax assets for tax attributes it believed will expire unused. The Company updated its Section 382 analysis through December 31, 2018 and confirmed there were no ownership changes since July 31, 2015. In the future, the Company may complete financings that could result in a change in control, which the Company will reduce its deferred tax assets for tax attributes it believes will expire unused due to the change in control limitations.

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

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2018 and 2017, the Company had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized in the Company's statements of operations and comprehensive loss.

The Company or one of its subsidiaries files income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2015 through December 31, 2018. To the extent the Company has tax attribute

carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, state or foreign tax authorities to the extent utilized in a future period.

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**Table of Contents****13. Convertible Senior Notes*****3.00% Convertible Senior Notes due 2025***

On October 16, 2018, the Company completed an offering of \$150,000 aggregate principal amount of the Company's 3.00% convertible senior notes due 2025 (the "Notes"). In addition, on October 26, 2018, the Company issued an additional \$22,500 aggregate principal amount of the Notes pursuant to the full exercise of the option to purchase additional Notes granted to the initial purchasers in the offering. The Notes were sold in a private offering to qualified institutional buyers in reliance on Rule 144A under the Securities Act. In accordance with accounting guidance for debt with conversion and other options, the Company separately accounted for the liability component ("Liability Component") and the embedded conversion option ("Equity Component") of the Notes by allocating the proceeds between the Liability Component and Equity Component, due to the Company's ability to settle the Notes in cash, common stock or a combination of cash and common stock, at its option. In connection with the issuance of the Notes, the Company incurred approximately \$5,615 of debt issuance costs, which primarily consisted of underwriting, legal and other professional fees, and allocated these costs between the Liability Component and the Equity Component based on the allocation of the proceeds. Of the total debt issuance costs, \$2,209 was allocated to the Equity Component and recorded as a reduction to additional paid-in capital and \$3,407 was allocated to the Liability Component and is recorded as a reduction of the Notes in the Company's consolidated balance sheets. The portion allocated to the Liability Component is amortized to interest expense using the effective interest method over seven years.

The Notes are senior unsecured obligations of the Company and bear interest at a rate of 3.00% per year payable semiannually in arrears on April 15 and October 15 of each year, beginning on April 15, 2019. Upon conversion, the Notes will be convertible into cash, shares of the Company's common stock or a combination of cash and shares of the Company's common stock, at the Company's election. The Notes will be subject to redemption at the Company's option, on or after October 15, 2022, in whole or in part, if the conditions described below are satisfied. The Notes will mature on October 15, 2025, unless earlier converted, redeemed or repurchased in accordance with their terms. Subject to satisfaction of certain conditions and during the periods described below, the Notes may be converted at an initial conversion rate of 63.0731 shares of common stock per \$1 principal amount of the Notes (equivalent to an initial conversion price of approximately \$15.85 per share of common stock).

Holders of the Notes may convert all or any portion of their notes, in multiples of \$1 principal amount, at their option at any time prior to the close of business on the business day immediately preceding June 15, 2025 only under the following circumstances:

- (1) during any calendar quarter commencing after the calendar quarter ending on December 31, 2018 (and only during such calendar quarter), if the last reported sale price of the Company's common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on, and including, the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price for the notes on each applicable trading day;
- (2) during the five business day period immediately after any five consecutive trading day period (the "Measurement Period") in which the trading price per \$1,000 principal amount of notes for each trading day of the Measurement Period was less than 98% of the product of the last reported sale price of the Company's common stock and the conversion rate on each such trading day;

(3) if the Company calls the notes for redemption, until the close of business on the business day immediately preceding the redemption date; or

(4) upon the occurrence of specified corporate events as described within the indenture.

As of December 31, 2018, none of the above circumstances had occurred and as such, the Notes could not have been converted.

**Table of Contents**

The Company may not redeem the Notes prior to October 15, 2022. On or after October 15, 2022, the Company may redeem for cash all or part of the Notes at its option if the last reported sale price of the common stock equals or exceeds 130% of the conversion price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending within five trading days prior to the date on which the Company sends any notice of redemption. The redemption price will be 100% of the principal amount of the Notes to be redeemed, plus accrued and unpaid interest, if any. In addition, calling any convertible note for redemption will constitute a make-whole fundamental change with respect to that convertible note, in which case the conversion rate applicable to the conversion of that convertible note, if it is converted in connection with the redemption, will be increased in certain circumstances.

The initial carrying amount of the Liability Component of \$101,243 was calculated by measuring the fair value of a similar liability that does not have an associated convertible feature. The allocation was performed in a manner that reflected the Company's non-convertible borrowing rate for similar debt. The Equity Component of the Notes of \$67,850 was recognized as a debt discount and represents the difference between the proceeds from the issuance of the Notes of \$172,500 and the fair value of the liability of the Notes of approximately \$104,650 on their respective dates of issuance. The excess of the principal amount of the Liability Component over its carrying amount is amortized to interest expense using the effective interest method over seven years. The Equity Component is not remeasured as long as it continues to meet the conditions for equity classification.

The outstanding balances of the Notes as of December 31, 2018 consisted of the following (in thousands):

|   |                  |
|---|------------------|
| <b>Liability component:</b>                 |                  |
| Principal                                   | \$ 172,500       |
| Less: debt discount and issuance costs, net | (69,836)         |
| Net carrying amount                         | \$ 102,664       |
| <b>Equity component:</b>                    | <b>\$ 70,059</b> |

The Company determined the expected life of the Notes was equal to its seven-year term. The effective interest rate on the Liability Component of the Notes was 11.85%. As of December 31, 2018, the if-converted value did not exceed the remaining principal amount of the Notes. The fair value of the Notes was determined based on data points other than quoted prices that are observable, either directly or indirectly, and has been classified as Level 2 within the fair value hierarchy. The fair value of the Notes, which differs from their carrying value, is influenced by market interest rates, the Company's stock price and stock price volatility. The estimated fair value of the Notes as of December 31, 2018 was approximately \$151,189.

The following table sets forth total interest expense recognized related to the Notes during the year ended December 31, 2018 (in thousands):

|                               | <b>Year Ended<br/>December 31, 2018</b> |
|-------------------------------|---|
| Contractual interest expense  | \$ 1,078                                |
| Amortization of debt discount | 1,353                                   |

|                                     |    |       |
|-------------------------------------|----|-------|
| Amortization of debt issuance costs |    | 68    |
| Total interest expense              | \$ | 2,499 |



**Table of Contents**

Future minimum payments on the Notes as of December 31, 2018 were as follows (in thousands):

| <b>Years ended December 31,</b> | <b>Future Minimum Payments</b> |          |
|---------------------------------|--------------------------------|----------|
| 2019                            | \$                             | 5,175    |
| 2020                            |                                | 5,175    |
| 2021                            |                                | 5,175    |
| 2022                            |                                | 5,175    |
| 2023 and thereafter             |                                | 188,025  |
| Total minimum payments          | \$                             | 208,725  |
| Less: interest                  |                                | (36,225) |
| Less: unamortized discount      |                                | (69,836) |
| Less: current portion           |                                |          |
| Long Term Debt                  | \$                             | 102,664  |

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

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

| <b>Year Ended December 31, 2018</b>   | <b>First<br/>Quarter</b> | <b>Second<br/>Quarter</b> | <b>Third<br/>Quarter</b> | <b>Fourth<br/>Quarter</b> |
|---------------------------------------|--------------------------|---------------------------|--------------------------|---------------------------|
| License and other revenue             | \$ 10,000                | \$ 19,891                 | \$ 239                   | \$ 206                    |
| Total operating expenses              | \$ 48,942                | \$ 54,223                 | \$ 49,393                | \$ 57,661                 |
| Loss from operations                  | \$ (38,942)              | \$ (34,332)               | \$ (49,154)              | \$ (57,455)               |
| Total other income (expense)          | \$ 483                   | \$ 677                    | \$ 1,071                 | \$ (755)                  |
| Net loss                              | \$ (38,459)              | \$ (33,655)               | \$ (48,083)              | \$ (58,210)               |
| Net loss per share, basic and diluted | \$ (0.78)                | \$ (0.60)                 | \$ (0.79)                | \$ (0.96)                 |
| <b>Year Ended December 31, 2017</b>   | <b>First<br/>Quarter</b> | <b>Second<br/>Quarter</b> | <b>Third<br/>Quarter</b> | <b>Fourth<br/>Quarter</b> |
| License and other revenue             | \$ 68                    | \$ 3                      | \$                       | \$ 1,534                  |
| Total operating expenses              | \$ 30,347                | \$ 29,755                 | \$ 31,055                | \$ 40,986                 |
| Loss from operations                  | \$ (30,279)              | \$ (29,752)               | \$ (31,055)              | \$ (39,452)               |
| Total other income (expense)          | \$ 385                   | \$ 383                    | \$ 428                   | \$ 421                    |
| Net loss                              | \$ (29,917)              | \$ (29,387)               | \$ (30,640)              | \$ (39,040)               |
| Net loss per share, basic and diluted | \$ (0.71)                | \$ (0.64)                 | \$ (0.65)                | \$ (0.80)                 |

**Table of Contents****EXHIBIT INDEX**

| <b>Exhibit Number</b> | <b>Description of Exhibit</b>  |
|-----------------------|--|
| 3.1                   | <u>Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 18, 2013)</u>   |
| 3.2                   | <u>Amended and Restated By-Laws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 18, 2013)</u>  |
| 4.1                   | <u>Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)</u>   |
| 4.2                   | <u>Third Amended and Restated Investors' Rights Agreement dated as of July 26, 2013 (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)</u>   |
| 4.3                   | <u>Indenture (including form of Note) with respect to the Registrant's 3.00% convertible senior notes due 2025, dated as of October 16, 2018, between the Registrant and Wilmington Trust, National Association, as trustee (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on October 16, 2018)</u> |
| 10.1*                 | <u>2010 Stock Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)</u>   |
| 10.2*                 | <u>Forms of Non-Qualified Stock Option Agreement under 2010 Stock Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)</u>   |
| 10.3*                 | <u>2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)</u>   |
| 10.4*                 | <u>Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)</u>  |
| 10.5*                 | <u>Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)</u>   |
| 10.6*                 | <u>Form of Restricted Stock Unit Agreement under the 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)</u>  |

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- 10.7\* Form of Nonstatutory Stock Option Agreement for Inducement Grants (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 10, 2018)
- 10.8\* 2013 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)
- 10.9\* Form of Indemnification Agreement between the Registrant and each of its Directors (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)

**Table of Contents**

| <b>Exhibit Number</b> | <b>Description of Exhibit</b>  |
|-----------------------|--|
| 10.10*                | <u>Managing Director Agreement, dated October 15, 2014, by and between Karyopharm Europe GmbH and Ran Frenkel (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015)</u>                     |
| 10.11*                | <u>Letter Agreement, dated October 15, 2014, by and between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015)</u>  |
| 10.12*                | <u>Amended and Restated Letter Agreement, dated as of January 23, 2015, between the Registrant and Michael Kauffman, M.D., Ph.D. (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 23, 2015)</u> |
| 10.13*                | <u>Amended and Restated Letter Agreement, dated as of January 23, 2015, between the Registrant and Sharon Shacham, Ph.D., M.B.A. (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 23, 2015)</u> |
| 10.14*                | <u>Amendment to Managing Director Agreement, dated February 15, 2015, by and between Karyopharm Europe GmbH and Ran Frenkel (incorporated by reference to Exhibit 10.22 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015)</u>       |
| 10.15*                | <u>Offer Letter, dated June 7, 2015, between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on June 10, 2015)</u>   |
| 10.16*                | <u>First Amendment to Letter Agreement, dated October 4, 2016, between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 16, 2017)</u>                             |
| 10.17*                | <u>Amended and Restated Letter Agreement, dated as of September 18, 2015, between the Registrant and Christopher B. Primiano (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)</u>  |
| 10.18*                | <u>Amendment to Managing Director Agreement, dated October 16, 2015, between Karyopharm Europe GmbH and Ran Frenkel (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)</u>           |
| 10.19*                | <u>Offer Letter, dated September 9, 2017, between the Registrant and Michael Falvey (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on September 12, 2017)</u>  |
| 10.20*                | <u>Offer Letter, dated June 7, 2018, between the Registrant and Anand Varadan (incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018)</u>   |
| 10.21*                | <u>Separation Agreement dated as of January 17, 2019, between the Registrant and Michael Falvey (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form</u>  |

8-K (File No. 001-36167) filed with the Commission on January 18, 2019)

10.22\*

Consulting Agreement, dated as of January 18, 2019, between the Registrant and Michael Falvey (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 18, 2019)

**Table of Contents**

| <b>Exhibit<br/>Number</b> | <b>Description of Exhibit</b>  |
|---------------------------|--|
| 10.23*                    | <u>Nonstatutory Stock Option Agreement, dated September 9, 2017, between the Registrant and Michael Falvey (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on September 12, 2017)</u>   |
| 10.24                     | <u>Office Lease Agreement between NS Wells Acquisition LLC and the Registrant, dated March 27, 2014 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on April 1, 2014)</u>   |
| 10.25                     | <u>First Amendment to Lease, dated December 31, 2014, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 5, 2015)</u>  |
| 10.26                     | <u>Second Amendment to Lease, dated October 22, 2015, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)</u>  |
| 10.27                     | <u>Third Amendment to Lease, dated February 28, 2018, by and between the Registrant and AG-JCM Wells Avenue Property Owner, LLC (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 10, 2018)</u>   |
| 10.28                     | <u>Fourth Amendment to Lease, dated June 6, 2018, by and between the Registrant and AG-JCM Wells Avenue Property Owner, LLC (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018)</u>   |
| 10.29                     | <u>Research Agreement, dated as of July 18, 2011, between the Registrant and the Multiple Myeloma Research Foundation, Inc. (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)</u>   |
| 10.30                     | <u>Controlled Equity Offering<sup>SM</sup> Sales Agreement, dated December 7, 2015, by and between the Registrant and Cantor Fitzgerald &amp; Co. (incorporated by reference to Exhibit 1.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 8, 2015)</u>   |
| 10.31                     | <u>Amendment No. 1 to Controlled Equity Offering<sup>SM</sup> Sales Agreement, dated December 7, 2015, by and between the Registrant and Cantor Fitzgerald &amp; Co., dated November 7, 2016 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 8, 2016)</u>                                 |
| 10.32                     | <u>Amendment No. 2 to Controlled Equity Offering<sup>SM</sup> Sales Agreement, dated December 7, 2015, as amended on November 7, 2016, by and between the Registrant and Cantor Fitzgerald &amp; Co., dated December 1, 2017 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 1, 2017)</u> |
| 10.33                     | <u>Open Market Sale Agreement<sup>SM</sup>, dated August 17, 2018, by and between the Registrant and Jefferies LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 17, 2018)</u>  |
| 10.34                     |  |

License Agreement, dated October 11, 2017, by and between the Registrant and Ono Pharmaceutical Co., Ltd. (incorporated by reference to Exhibit 10.30 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 15, 2018)

**Table of Contents**

| <b>Exhibit<br/>Number</b> | <b>Description of Exhibit</b>   |
|---------------------------|---|
| 10.35                     | <u>Asset Purchase Agreement, dated January 24, 2018, by and between the Registrant and Biogen MA Inc. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 10, 2018</u>   |
| 10.36                     | <u>License Agreement, dated May 23, 2018, by and between the Registrant and Antengene Therapeutics Limited (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018</u>  |
| 10.37                     | <u>Parent Company Guarantee, dated May 23, 2018, by and between the Registrant and Antengene Therapeutics Limited (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018</u>   |
| 21.1**                    | <u>Subsidiaries of the Registrant</u>   |
| 23.1**                    | <u>Consent of Ernst &amp; Young LLP (Independent registered public accounting firm for the Company)</u>   |
| 31.1**                    | <u>Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>   |
| 31.2**                    | <u>Certification of Vice President, Finance and Assistant Treasurer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>   |
| 32.1**                    | <u>Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by Michael G. Kauffman, M.D., Ph.D., Chief Executive Officer of the Registrant, and Cameron Peters, Vice President, Finance and Assistant Treasurer (<i>Principal Financial and Accounting Officer</i>) of the Registrant</u> |
| 101.INS XBRL              | Instance Document   |
| 101.SCH XBRL              | Schema Document   |
| 101.CAL XBRL              | Calculation Linkbase Document   |
| 101.LAB XBRL              | Labels Linkbase Document  |
| 101.PRE XBRL              | Presentation Linkbase Document  |
| 101.DEF XBRL              | Definition Linkbase Document  |

Confidential treatment has been granted as to portions of the exhibit.

\* Indicates a management contract or compensatory plan or arrangement.

\*\* Filed with this Annual Report on Form 10-K.



Table of Contents**SIGNATURES**

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

**KARYOPHARM THERAPEUTICS INC.**

Date: February 28, 2019

By: /s/ Michael G. Kauffman  
Michael G. Kauffman, M.D., Ph.D.

*Chief Executive Officer and Director*

*(Principal Executive Officer)*

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

| <b>Signature</b>  | <b>Title</b>   | <b>Date</b>       |
|---|--|-------------------|
| /s/ Michael G. Kauffman<br>Michael G. Kauffman, M.D., Ph.D. | Chief Executive Officer and Director<br><i>(Principal Executive Officer)</i>                           | February 28, 2019 |
| /s/ Cameron Peters<br>Cameron Peters                        | Vice President, Finance and Assistant Treasurer<br><i>(Principal Financial and Accounting Officer)</i> | February 28, 2019 |
| /s/ Garen G. Bohlin<br>Garen G. Bohlin                      | Director   | February 28, 2019 |
| /s/ Mikael Dolsten<br>Mikael Dolsten, M.D., Ph.D.           | Director   | February 28, 2019 |
| /s/ J. Scott Garland<br>J. Scott Garland                    | Director   | February 28, 2019 |
| /s/ Barry E. Greene<br>Barry E. Greene                      | Director   | February 28, 2019 |
| /s/ Deepika R. Pakianathan<br>Deepika R. Pakianathan, Ph.D. | Director   | February 28, 2019 |
| /s/ Mansoor Raza Mirza<br>Mansoor Raza Mirza, M.D.          | Director   | February 28, 2019 |