Onconova Therapeutics, Inc.
Form 10-K
March 16, 2018

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark one)

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

For the fiscal year ended December 31, 2017

Or

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

For the transition period from to
Commission file number 001-36020

Onconova Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**22-3627252**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
375 Pheasant Run, Newtown, PA	**18940**
(Address of principal executive offices)	(Zip Code)

(267) 759-3680
(Registrant's telephone number, including area code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $.01 per share	The Nasdaq Stock Market LLC

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ý No o

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 o	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company ý
			Emerging growth company ý

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. o

Indicate by check mark whether the registrant is a shell company (as defined in Rule12b-2 of the Act). Yes o No ý

As of June 30, 2017, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's voting stock held by non-affiliates was approximately $17.8 million, based on the last reported sale price of the registrant's common stock on the Nasdaq Capital Market.

There were 18,946,163 shares of Common Stock outstanding as of March 1, 2018.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for the registrant's 2018 annual meeting of stockholders to be filed within 120 days after the end of the period covered by this annual report on Form 10-K are incorporated by reference into Part III of this annual report on Form 10-K.

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All common stock, equity, share and per share amounts have been retroactively adjusted to reflect a one-for-ten reverse stock split which was effective May 31, 2016.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K ("Annual Report") includes forward-looking statements. We may, in some cases, use terms such as "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements appear in a number of places throughout this Annual Report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, protection of our intellectual property portfolio, the degree of clinical utility of our products, particularly in specific patient populations, our ability to develop commercial and manufacturing functions, expectations regarding clinical trial data, our results of operations, cash needs, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Annual Report.

You should also read carefully the factors described in the "Risk Factors" section of this Annual Report and elsewhere to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements in this report and you should not place undue reliance on any forward-looking statements. These factors include, without limitations, the risks related to:

- our need for additional financing for our INSPIRE trial and other operations, and our ability to obtain sufficient funds on acceptable terms when needed, and our plans and future needs to scale back operations if adequate financing is not obtained;
- our ability to continue as a going concern;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- the success and timing of our preclinical studies and clinical trials, including site initiation and patient enrollment, and regulatory approval of protocols for future clinical trials;
- our ability to enter into, maintain and perform collaboration agreements with other pharmaceutical companies, for funding and commercialization of our clinical drug product candidates or preclinical compounds, and our ability to achieve certain milestones under those agreements;
- the difficulties in obtaining and maintaining regulatory approval of our product candidates, and the labeling under any approval we may obtain;
- our plans and ability to develop, manufacture and commercialize our product candidates;
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;

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the size and growth of the potential markets for our product candidates and our ability to serve those markets;

regulatory developments in the United States and foreign countries;

the rate and degree of market acceptance of any of our product candidates;

obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;

the successful development of our commercialization capabilities, including sales and marketing capabilities;

recently enacted and future legislation and regulation regarding the healthcare system;

the success of competing therapies and products that are or may become available;

our ability to maintain the listing of our securities on a national securities exchange;

the potential for third party disputes and litigation; and

the performance of third parties, including contract research organizations ("CROs") and third-party manufacturers.

Any forward-looking statements that we make in this Annual Report speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this Annual Report or to reflect the occurrence of unanticipated events.

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PART I

ITEM 1. *BUSINESS*

Overview

Onconova Therapeutics, Inc., sometimes referred to as "we" or the "Company," is a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule product candidates primarily to treat cancer. Using our proprietary chemistry platform, we have created a library of targeted agents designed to work against cellular pathways important to cancer cells. We believe that the product candidates in our pipeline have the potential to be efficacious in a variety of cancers. We have one Phase 3 clinical-stage product candidate and two other clinical-stage product candidates (one of which is being developed for treatment of acute radiation syndromes) and several preclinical programs. Substantially all of our current effort is focused on our lead product candidate, rigosertib. Rigosertib is being tested in an intravenous formulation as a single agent, and an oral formulation in combination with azacitidine, in clinical trials for patients with higher-risk myelodysplastic syndromes ("MDS"). The Company has and may continue to delay, scale-back, or eliminate certain of its research and development activities and other aspects of its operations until such time as the Company is successful in securing additional funding.

In December 2015, we enrolled the first patient into our INSPIRE trial, a randomized controlled Phase 3 clinical trial of intravenous rigosertib ("rigosertib IV") in a population of patients with higher-risk MDS after failure of hypomethylating agent ("HMA") therapy. The primary endpoint of INSPIRE is overall survival. An interim analysis of the trial was performed in January 2018 and we anticipate reporting topline data from the INSPIRE trial in the first half of 2019.

Myelodysplastic Syndromes

MDS is a group of blood disorders that affect bone marrow function. MDS typically affects older patients. In MDS, the bone marrow cells appear dysplastic, and their capacity to produce cells is defective. Therefore, blood cells do not develop normally, such that too few healthy blood cells are released into the blood stream, leading to low blood cell counts, or cytopenias. Thus, many patients with MDS require frequent blood transfusions. In most cases, the disease worsens and the patient develops progressive bone marrow failure. In advanced stages of the disease, immature blood cells, or blasts, leave the bone marrow and enter the blood stream, leading to acute myelogenous leukemia ("AML"), which occurs in approximately one-third of patients with MDS.

Based on Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute, a marketing analytics firm has estimated the 2016 incidence of MDS to be approximately 17,390 cases and the prevalence of MDS to be approximately 61,690 cases in the United States. We believe that the actual incidence numbers may be higher, due to underdiagnosing and underreporting of new cases of MDS to centralized cancer registries, and that the incidence of MDS in the United States is likely to increase, due to an aging population, improved disease awareness and diagnostic precision, and an increase in the number of cases of secondary, often chemotherapy-induced, MDS.

MDS is typically diagnosed using routine blood tests or by observing a combination of certain symptoms, such as shortness of breath, weakness, easy bruising or bleeding, or fever with frequent infections. A diagnosis of MDS is confirmed by evaluating a bone marrow biopsy/aspirate showing dysplastic changes, and, in more advanced cases, the presence of excess blasts, meaning that blasts account for more than 5% of the total number of nucleated cells in the bone marrow. Several classification systems have been developed to gauge the severity of disease and help determine prognosis and treatment strategy. Two standard classification systems can be used, the French-American-British morphological classification system as modified by the World Health Organization, or WHO, and the recently revised International Prognostic Scoring System ("IPSS-R") to estimate

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anticipated survival for patients with MDS based on marrow function and marrow cytogenetics. IPSS-R ranks the severity of chromosome abnormalities, severity of cytopenias, and percentage of bone marrow blasts observed at diagnosis to calculate a five-level risk score: Very Low, Low, Intermediate, High and Very High. MDS patients are generally classified using IPSS-R in order to assess the risk of dying or having their disease progress to AML.

Treating Myelodysplastic Syndromes

We believe that most higher-risk and some lower-risk MDS patients in the United States are treated with azacitidine or decitabine, the two approved HMAs for treatment of MDS. A provider of information services and technology for the healthcare industry estimates that in the year ended June 2012, approximately 12,500 MDS patients in the United States received treatment with HMAs.

A significant number of higher-risk MDS patients fail or cannot tolerate treatment with azacitidine or decitabine, which represent the current standard of care for higher-risk MDS patients, and almost all patients who initially respond to therapy eventually progress. Median survival time of higher-risk MDS patients who have failed HMAs is less than one year. Accordingly, we believe that a new therapy that would extend survival in these patients would represent a major contribution in the treatment of MDS.

Allogeneic peripheral blood stem cell or bone marrow transplantation is a potentially curative therapy for MDS. However, since most patients with MDS are elderly and therefore ineligible for transplantation due to the arduous nature of the procedure, this option is generally considered only for the small proportion of younger MDS patients.

HMAs are believed to inhibit the methylation of DNA. Methylation is a biochemical process involving the addition of a methyl group to DNA and plays an important role in gene expression during cell division and differentiation. Hypomethylation may also restore normal function to genes that are critical for differentiation and proliferation. By contrast, rigosertib is designed to block multiple oncogenic pathways through a RAS mimetic mechanism and/or interfering with RAS function. Because we believe rigosertib has a mechanism of action that is different from HMAs, it may be active in patients who have failed treatment with those drugs. Furthermore, rigosertib's distinct potential mechanism of action has been shown to combine well with approved HMAs and preclinical studies testing the combination of rigosertib with azacitidine have demonstrated synergy between the two agents. Based on these studies and our current understanding of the potential mechanism of action of rigosertib, we believe that rigosertib also has the potential to be developed in combination with azacitidine for first line or second line MDS patients and for patients with AML who are not candidates for standard induction chemotherapy; or second-line AML who have failed induction chemotherapy.

Lower-risk MDS patients are those categorized as Very Low, Low or possibly Intermediate risk by the IPSS-R scoring system, with transfusion-dependent anemia. The subset of del(5q) cytogenetic abnormality patients are generally treated with lenalidomide (Revlimid®). For all other lower-risk MDS patients, supportive care employing blood products, such as red blood cell and platelet transfusions, and erythroid stimulating agents, is the mainstay of therapy. Frequent transfusions introduce many risks, including iron overload, blood borne infections and immune-related reactions. We believe that an oral therapeutic agent that could lower or eliminate the need for transfusions over an extended period of time for the lower-risk population as a whole and would fulfill a significant unmet medical need for this patient population.

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Our Product and Product Candidates

Rigosertib

Rigosertib is a small molecule which we believe blocks cellular signaling by targeting RAS effector pathways. This is believed to be mediated by the interaction of rigosertib to the RAS-binding domain ("RBD"), found in many RAS effector proteins, including the Raf and PI3K kinases. We believe this mechanism of action provides a new approach to block the interactions between RAS and its targets containing RBD sites. Rigosertib is currently being tested in clinical trials as a single agent, and in combination with azacitidine, in patients with MDS. We have enrolled more than 1,300 patients in rigosertib clinical trials for MDS and other conditions. We were a party to a license and development agreement with Baxalta (as defined below), which granted Baxalta certain rights to commercialize rigosertib in Europe. The Baxalta agreement was terminated on August 30, 2016, at which time the European rights reverted to us at no cost. We are party to a collaboration agreement with SymBio, which grants SymBio certain rights to commercialize rigosertib in Japan and Korea. We have retained development and commercialization rights to rigosertib in the rest of the world, including in the United States and Europe, although we could consider licensing commercialization rights to other territories as we continue to seek additional funding. Previously we were a party to a license and development agreement with Baxalta (as defined below), which granted Baxalta certain rights to commercialize rigosertib in Europe. The Baxalta agreement was terminated on August 30, 2016, at which time the European rights reverted to us at no cost.

The table below summarizes our rigosertib clinical stage programs.

Rigosertib IV for higher-risk MDS

We are developing an IV version of rigosertib for the treatment of higher-risk MDS following the failure of HMA therapy. In early 2014, we announced topline survival results from our "ONTIME" trial, a multi-center Phase 3 clinical trial of rigosertib IV as a single agent versus best supportive care including low dose Ara-C. The ONTIME trial did not meet its primary endpoint of an improvement in overall survival in the intent-to-treat population, although improvements in median overall survival were observed in various pre-specified and exploratory subgroups of higher-risk MDS patients. As a result, additional clinical work is on-going.

During 2014 and 2015, we held meetings with the U.S. Food and Drug Administration ("FDA"), European Medicines Agency ("EMA"), and several European national regulatory authorities to discuss and seek guidance on a path for approval of rigosertib IV in higher-risk MDS patients whose disease

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had failed HMA therapy. After discussions with the FDA and EMA, we refined our patient eligibility criteria by defining what we believe to be a more homogenous patient population. After regulatory feedback, input from key opinion leaders in the U.S. and Europe and based on learnings from the ONTIME study, we designed a new randomized controlled Phase 3 trial, referred to as INSPIRE. The INSPIRE trial is enrolling higher-risk MDS patients under 82 years of age who have progressed on, relapsed, or failed to respond to, previous treatment with HMAs within nine months or nine cycles over the course of one year after initiation of HMA therapy, and had their last dose of HMA within six months prior to enrollment in the trial. Patients are randomized to either rigosertib with best supportive care, or the physician's choice of therapy with best supportive care. The primary endpoint of this study is the sequential analysis of overall survival of all randomized patients in the intent-to-treat ("ITT") population and the International Prognostic Scoring System- Revised (IPSS-R) Very High Risk subgroup. The first patient in the INSPIRE trial was enrolled at the MD Anderson Cancer Center in December 2015, the first patient in Europe was enrolled in March, 2016, and the first patient in Japan was enrolled in July, 2016.

Enrollment for the INSPIRE Phase 3 trial for second-line higher-risk MDS patients is highly selective with stringent entry criteria as outlined above. Currently, the INSPIRE study has opened approximately 175 trial sites in 22 countries across four continents, and has enrolled more than 170 patients. Our partner, SymBio Pharmaceuticals, has opened more than 30 sites in Japan. The selection of countries and trial sites is carefully undertaken to ensure availability of appropriate patients meeting eligibility criteria. Since these criteria are purposely designed to be narrow and selective, extensive site screening and education is integral to our plan. At launch, the INSPIRE trial was expected to enroll 225 patients and the outcome is measured by overall survival.

The INSPIRE trial included a pre-planned interim analysis triggered by 88 events (deaths), which occurred in December 2017. The statistical analysis plan ("SAP") for the INSPIRE trial featured an adaptive trial design, permitting several options following the interim analysis, which included continuation of the trial as planned, discontinuation of the trial for futility or safety, trial expansion using pre-planned sample size re-estimation, and trial continuation for only the pre-defined treatment subgroup of patients classified as Very High Risk ("VHR") based on the IPSS-R.

After review of the interim data, in January 2018 the Independent Data Monitoring Committee ("DMC") recommended continuation of the trial with a one-time expansion in enrollment, using a pre-planned sample size re-estimation, consistent with the SAP. As recommended by the DMC, the expanded INSPIRE study will continue to enroll eligible patients based on the current trial criteria of the overall ITT population and will increase enrollment by adding 135 patients to the original target to reach a total enrollment of 360 patients, with the aim of increasing the power of the trial. Due to the adaptive trial design and the DMC's assessment, the INSPIRE trial will continue to analyze both the ITT and the VHR population for the primary endpoint of overall survival. The design of the trial with the expanded study enrollment will be identical to the current study design and will include the sequential analysis of the overall survival endpoint in the ITT population and if required the pre-specified VHR subgroup. The Company remains blinded to the specific interim analysis results. We anticipate reporting topline data from the INSPIRE trial in the first half of 2019.

Safety and Tolerability of rigosertib in MDS and other hematologic malignancies

A comprehensive analysis of IV and rigosertib oral safety in patients with Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) was presented in December 2016 at the American Society of Hematology (ASH) Annual Meeting. The most commonly reported treatment-emergent adverse events (TEAEs) in ≥ 10% of patients with MDS/AML (n= 335) receiving rigosertib intravenous (IV) monotherapy were fatigue (33%), nausea (33%), diarrhea (27%), constipation (25%), anaemia (24%) and pyrexia (24%). The most common ≥ Grade 3 AEs were anaemia (21%), febrile neutropenia (13%), pneumonia (12%) and thrombocytopenia (11%). The most common serious AEs were febrile neutropenia (10%), pneumonia (9%), and sepsis (7%). The most common AEs leading to discontinuation of IV rigosertib were sepsis and pneumonia (3% each).

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Rigosertib oral in combination with azacitidine for higher-risk MDS

We are developing rigosertib oral for use in combination with azacitidine prior to treatment with HMA therapy for higher risk MDS. In December 2016, at the American Society of Hematology (ASH) Annual Meeting, we presented Phase 1/2 data from a rigosertib oral and azacitidine combination trial in higher-risk MDS. 33 of 40 MDS patients enrolled were evaluable for response at the time of the analysis. The median age of patients was 66, with 73% being male. The IPSS-R distribution was: 7.5% Low, 12.5% Intermediate, 37.5% High, 32.5% Very High and 10% unknown. 76% of patients responded per 2006 International Working Group (IWG) criteria. Responses were as follows:

Response per IWG 2006

	Overall Evaluable (N=33)	**No prior HMA (N-20)**	**Prior HMA (N=13)**
Complete remission (CR)	8(24)%	7(35)%	1(8)%
Marrow CR + hematologic improvement	10(30)%	6(30)%	4(31)%
Marrow CR alone	6(18)%	3(15)%	3(23)%
Hematologic improvement alone	1(3)%	1(5)%	0
Stable disease	8(24)%	3(15)%	5(38)%
Overall IWG response	25(76)%	17(85)%	8(62)%
Clinical benefit response	19(58)%	14(70)%	5(38)%

The median duration of response was 8 months for CR, 12.3 months for marrow CR.

Safety/Tolerability of the Combination:

Rigosertib oral (560 mg qAM, 280 mg qPM; total of 840 mg of oral rigosertib) was administered on Day 1-21 of a 28-day cycle. Azacitidine 75 mg/m 2 /day SC or IV was administered for 7 days starting on Day 8. The combination of rigosertib oral and azacitidine was well tolerated. The most common TEAEs in ≥ 10% of patients with MDS/AML (n=54) receiving rigosertib oral and azacitidine were nausea (41%), fatigue (39%), diarrhea (37%), constipation (37%) and dysuria (28%). The most common serious AEs were pneumonia (11%) and febrile neutropenia (7%). The most common AEs leading to discontinuation were AML (4%) and pneumonia (4%).

Next steps for rigosertib oral in combination with azacitidine for higher-risk MDS

Following an end of Phase 2 meeting with the Food and Drug Administration (FDA) in September 2016, we began development of a Phase 3 protocol. The Phase 3 trial will be designed as a global 1:1 randomized, placebo-controlled trial of rigosertib oral plus azacitidine compared to azacitidine plus oral placebo. Based on the results of the Phase 1/2 Study, full dose of azacitidine will be used in combination with rigosertib oral, as defined in the product insert for azacitidine. The patient population studied in this trial will be first-line (HMA naïve) higher-risk MDS patients. The primary endpoint for assessment of efficacy will be the composite Response Rate of complete remission (CR) + partial remission (PR,) as per the IWG 2006 Response Criteria. The trial will be under the review of a DMC. Formal FDA review may be sought via the Special Protocol Assessment (SPA) mechanism. We will not commence the Phase 3 trial without additional financing.

While the Phase 3 trial is being designed, we have expanded the Phase 2 trial cohort by up to 40 evaluable subjects. Under a protocol expansion, we plan to use the expanded cohorts to explore dose optimization by increasing the dose of rigosertib oral to a total of 1120 mg in combination with full dose azacitidine and varying the dose administration scheme of rigosertib oral to identify an optimal dose and schedule. After amendments were filed with the regulatory agencies, we started the expansion phase of this trial in the U.S. sites that participated in the initial trial. Since the trial initiation, we have

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added additional US sites to complete enrollment of the expanded trial. The first patient was enrolled in April 2017 and since then, more than half of the planned patients have been enrolled in the expansion trial; and the trial is ongoing.

In June 2017, at the Congress of the European Hematology Association Meeting, we updated the data from the Phase 1/2 trial and highlighted results in AML patients included in this study. Response data was presented on eight evaluable patients with AML who were tested with the rigosertib and azacitidine combination. For the eight evaluable patients with AML, the combination was well tolerated and the safety profile was similar to single-agent azacitidine, based on safety information in the azacitidine FDA approved label. Based on the presented results of the combination studies, the authors concluded that continued study in AML was warranted. We will not commence further development of rigosertib oral in combination with azacitidine for AML without additional financing.

Rigosertib oral for lower-risk MDS

We are also developing rigosertib oral as a single agent treatment for lower risk MDS. Higher-risk MDS patients suffer from a shortfall in normal circulating blood cells, or cytopenias, as well as elevated levels of cancer cells, or blasts in their bone marrow and sometimes in their peripheral blood with a significant rate of transformation to acute leukemia. Lower-risk MDS patients suffer mainly from cytopenias, that is low levels of red blood cells, white blood cells or platelets. Thus, lower-risk MDS patients depend on transfusions and growth factors or other therapies to improve their low blood counts; but have a lower rate of acute leukemic transformation.

We have explored single agent rigosertib oral as a treatment for lower-risk MDS in two Phase 2 clinical trials, 09-05 and 09-07. In December 2017, we presented data at the Annual ASH Meeting from the 09-05 Phase 2 trial. This data demonstrated a 44% rate of achieving transfusion independence in the cohort of Lower -risk MDS patients treated with rigosertib oral at a dose of 560 mg BID (1120 mg over 24 hrs). To date, Phase 2 clinical data has indicated that further study of single agent rigosertib oral in transfusion-dependent, lower-risk MDS patients is warranted. Rigosertib has been generally well tolerated, except for urinary side effects at higher dose levels. Future clinical trials will be needed to evaluate dosing and schedule modifications and their impact on efficacy and safety results of rigosertib oral in lower-risk MDS patients.

Data presented from the 09-05 trial also suggested the potential of a genomic methylation assessment of bone marrow cells to prospectively identify lower-risk MDS patients likely to respond to rigosertib oral. We therefore expanded the 09-05 trial by adding an additional cohort of 20 patients to advance the development of this genomic methylation test. To date, a biomarker which would predict response has not been identified. Further testing and development of rigosertib oral for lower-risk MDS will be required. We will not commence further development of rigosertib oral for lower-risk MDS without additional financing.

Safety and Tolerability of rigosertib oral in MDS and other hematologic malignancies

As presented at the December 2016 ASH Annual Meeting, rigosertib oral as a monotherapy was evaluated in four Phase 1 and 2 studies in MDS and other hematologic malignancies. One study is completed and a clinical study report is available. The most common TEAEs in ≥ 10% of patients with MDS/AML (n=168) were pollakiuria (increased urinary frequency) (35%), fatigue (32%), diarrhea (26%), dysuria (29%) and haematuria (24%). The most common ≥ Grade 3 AEs were anaemia (17%), thrombocytopenia (5%), haematuria (4%) and urinary tract infection (4%). The most common serious AE was pneumonia (6%). The most common AEs leading to discontinuation of patients receiving rigosertib oral as monotherapy were dysuria (8%), urinary tract pain (7%), haematuria (5%) and urinary frequency (5%).

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In addition to the above described clinical trials, we are continuing the preclinical and chemistry, manufacturing, and control work for IV and rigosertib oral.

Rare Disease Program in "RASopathies"

Based on new mechanism of action data published last year, we are initiating a collaborative development program focusing on a group of rare diseases with a well-defined molecular basis in expression or defects involving the Ras Effector Pathways. Since "RASopathies" are rare diseases affecting young children, we are embarking on a multifaceted collaborative program involving patient advocacy, government and academic organizations. The RASopathies are a group of rare diseases which share a well-defined molecular basis in expression or defects involving Ras Effector Pathways. They are usually caused by germline mutations in genes that alter the RAS subfamily and mitogen-activated protein kinases that control signal transduction, and are among the most common genetic syndromes. Together, this group of diseases can impact more than 1 in 1000 individuals, according to RASopathiesNet.

In January 2018, we entered into a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI), part of the National Institutes of Health (NIH). Under the terms of the CRADA, the NCI will conduct research, including preclinical laboratory studies and a clinical trial, on rigosertib in pediatric cancer associated RASopathies.

As part of the CRADA, we will provide rigosertib supplies and initial funding towards non-clinical studies. The NCI will fund the majority of the research, including the cost of the clinical trial, which is expected to start in 2018. A clinical trial protocol has been developed and will be reviewed by the Institutional Review Board.

While the NCI will conduct a trial for RASopathy related cancers in pediatric patients, we will focus on Juvenile Myelomonocytic Leukemia (JMML), a well-described RASopathy affecting children which is incurable without an allogenic hematopoietic stem cell transplant.

Other Programs

The vast majority of the Company's efforts are now devoted to the advanced stage development of rigosertib for unmet medical needs of MDS patients. Other programs are either paused, inactive or require only minimal internal resources and efforts.

Briciclib

Briciclib, another of our product candidates, is a small molecule targeting an important intracellular regulatory protein, Cyclin D1, which is often found at elevated levels in cancer cells. Cyclin D1 expression is regulated through a process termed cap-dependent translation, which requires the function of eukaryotic initiation factor 4E protein. In vitro evidence indicates briciclib binds to eukaryotic initiation factor 4E protein, blocking cap-dependent translation of Cyclin D1 and other cancer proteins, such as c-MYC, leading to tumor cell death. We have been conducting a Phase 1 multi-site dose-escalation trial of briciclib in patients with advanced solid tumors refractory to current therapies. Safety and efficacy assessments are complete in six of the seven dose-escalation cohorts of patients in this trial. As of December 2015, the Investigational New Drug ("IND") for briciclib is on full clinical hold following a drug product lot testing failure. We will be required to undertake appropriate remedial actions prior to re-initiating the clinical trial and completing the final dose-escalation cohort.

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Recilisib

Recilisib is a product candidate being developed in collaboration with the U.S. Department of Defense for acute radiation syndromes. We have completed four Phase 1 trials to evaluate the safety and pharmacokinetics of recilisib in healthy human adult subjects using both subcutaneous and oral formulations. We have also conducted animal studies and clinical trials of recilisib under the FDA's Animal Rule, which permits marketing approval for new medical countermeasures for which conventional human efficacy studies are not feasible or ethical, by relying on evidence from adequate and well-controlled studies in appropriate animal models to support efficacy in humans when the results of those studies establish that the drug is reasonably likely to produce a human clinical benefit. Human safety data, however, is still required. Ongoing studies of recilisib, focusing on animal models and biomarker development to assess the efficacy of recilisib are being conducted by third parties with government funding. We anticipate that any future development of recilisib beyond these ongoing studies would be conducted solely with government funding or by collaboration. Use of government funds to finance the research and development in whole or in part means any future effort to commercialize recilisib will be subject to federal laws and regulations on U.S. government rights in intellectual property. Additionally, we are subject to laws and regulations governing any research contracts, grants, or cooperative agreements under which government funding was provided.

Preclinical Product Candidates

In addition to our three clinical-stage product candidates, we have several product candidates that target kinases, cellular metabolism or cell division in preclinical development. We may explore additional collaborations to further the development of these product candidates as we focus internally on our more advanced programs.

Positive preclinical data was announced at the American Association for Cancer Research (AACR) annual meeting, which took place April 1-5, 2017 in Washington, DC, for ON 123300, a first-in-class dual inhibitor of CDK4/6 + ARK5, and for ON 150030, a novel Type 1 inhibitor of FLT3 and Src pathways. We believe our CDK inhibitor is differentiated from other agents in the market (Palbociclib, Ribociclib and Abemaciclig) or in development (such as the compounds being developed by G1 Therapeutics) by its dual inhibition of CDK4/6 + ARK5. We continue to carry out research to enhance the pre-clinical data package for this compound in an attempt to seek partners for co-development of this novel compound.

In a preclinical Rb+ve xenograft model for breast cancer, ON 123300 activity was shown to be similar to Palbociclib (Pfizer's Ibrance®). Moreover, based on the same preclinical model, the new molecule may have the potential advantage of reduced neutropenia when compared to Palbociclib. Whereas both compounds resulted in decreased RBC and platelet counts in this preclinical model system, Palbociclib was found to have a more prominent and statistically significant ($P< 0.05$) inhibitory effect on neutrophil counts when compared to ON 123300.

Research and Development

Since commencing operations, we have dedicated a significant portion of our resources to the development of our clinical-stage product candidates, particularly rigosertib. We incurred research and development expenses of $19.1 million, $20.1 million and $25.9 million during the years ended December 31, 2017, 2016 and 2015, respectively. We anticipate that a significant portion of our operating expenses will continue to be related to research and development.

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Collaboration and License Agreements

SymBio Pharmaceuticals Limited

In July 2011, we entered into a license agreement with SymBio, as subsequently amended, granting SymBio an exclusive, royalty-bearing license for the development and commercialization of rigosertib in Japan and Korea (the "SymBio Territory"). Under the SymBio license agreement, SymBio is obligated to use commercially reasonable efforts to develop and obtain market approval for rigosertib inside the licensed territory and we have similar obligations outside of the licensed territory. We have also entered into an agreement with SymBio providing for the Company to supply SymBio with development-stage product. Under the SymBio license agreement, we also agreed to supply commercial product to SymBio under specified terms that will be included in a commercial supply agreement to be negotiated prior to the first commercial sale of rigosertib. The supply of development-stage product and the supply of commercial product will be at our cost plus a defined profit margin. We have additionally granted SymBio a right of first negotiation to license or obtain the rights to develop and commercialize compounds having a chemical structure similar to rigosertib in the licensed territory.

Under the terms of the SymBio license agreement, we received an upfront payment of $7,500,000. We are eligible to receive milestone payments of up to an aggregate of $22,000,000 from SymBio upon the achievement of specified development and regulatory milestones for specified indications. Of the regulatory milestones, $5,000,000 is due upon receipt of marketing approval in the United States for rigosertib IV in higher-risk MDS patients, $3,000,000 is due upon receipt of marketing approval in Japan for rigosertib IV in higher-risk MDS patients, $5,000,000 is due upon receipt of marketing approval in the United States for rigosertib oral in lower-risk MDS patients, and $5,000,000 is due upon receipt of marketing approval in Japan for rigosertib oral in lower-risk MDS patients. Furthermore, upon receipt of marketing approval in the United States and Japan for an additional specified indication of rigosertib, which we are currently not pursuing, an aggregate of $4,000,000 would be due. In addition to these pre-commercial milestones, we are eligible to receive tiered milestone payments based upon annual net sales of rigosertib by SymBio of up to an aggregate of $30,000,000.

Further, under the terms of the SymBio license agreement, SymBio will make royalty payments to us at percentage rates ranging from the mid-teens to 20% based on net sales of rigosertib by SymBio.

Royalties will be payable under the SymBio agreement on a country-by-country basis in the licensed territory, until the later of the expiration of marketing exclusivity in those countries, a specified period of time after first commercial sale of rigosertib in such country, or the expiration of all valid claims of the licensed patents covering rigosertib or the manufacture or use of rigosertib in such country. If no valid claim exists covering the composition of matter of rigosertib or the use of or treatment with rigosertib in a particular country before the expiration of the royalty term, and specified competing products achieve a specified market share percentage in such country, SymBio's obligation to pay us royalties will continue at a reduced royalty rate until the end of the royalty term. In addition, the applicable royalties payable to us may be reduced if SymBio is required to pay royalties to third-parties for licenses to intellectual property rights necessary to develop, use, manufacture or commercialize rigosertib in the licensed territory. The license agreement with SymBio will remain in effect until the expiration of the royalty term. However, the SymBio license agreement may be terminated earlier due to the uncured material breach or bankruptcy of a party, or force majeure. If SymBio terminates the license agreement in these circumstances, its licenses to rigosertib will survive, subject to SymBio's milestone and royalty obligations, which SymBio may elect to defer and offset against any damages that may be determined to be due from us. In addition, we may terminate the license agreement in the event that SymBio brings a challenge against it in relation to the licensed patents, and SymBio may terminate the license agreement without cause by providing us with written notice a specified period of time in advance of termination.

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The upfront payment is being recognized ratably using the straight line method through December 2027, the expected term of the agreement. We recognized revenues under this agreement of $454,000 and $455,000, for the fiscal years ended December 31, 2017 and 2016, respectively. We recognized revenues related to the supply agreement with SymBio of $333,000 and $92,000 for the fiscal years ended December 31, 2017 and 2016, respectively.

SymBio has conducted phase 1 trials with IV and rigosertib oral in Japan at their own expense. Currently SymBio is participating in the INSPIRE trial by enrolling patients in Japan. For all rigosertib trials conducted by SymBio, we supply clinical trial supplies and provide other assistance as requested.

Baxalta GmbH

In September 2012, we entered into a development and license agreement with Baxter Healthcare SA, the predecessor in interest to Baxalta, pursuant to which we granted an exclusive, royalty-bearing license for the research, development, commercialization and manufacture (in specified instances) of rigosertib in all therapeutic indications in Europe. In accordance with this agreement, we received an upfront cash payment of $50,000,000 in 2012. On March 3, 2016, we received a notification of Baxalta's election to terminate the development and license agreement based on a strategic reprioritization review, effective August 30, 2016, at which time, the rights licensed to Baxalta reverted to us at no cost. Additionally, any rights we had to funding, pre-commercial milestone payments and royalties from Baxalta terminated in accordance with the agreement.

Among other things, the Baxalta agreement contemplated development of rigosertib IV in higher-risk MDS patients, through our ONTIME trial and, potentially, additional Phase 3 clinical trials. The ONTIME trial did not achieve its primary endpoint and we are continuing the development of rigosertib IV in higher-risk MDS patients through our INSPIRE trial. In accordance with the agreement, we elected to have Baxalta fund fifty percent of the costs of the INSPIRE trial, up to $15.0 million. We recorded revenue of $0 and $4,999,000 during the years ended December 31, 2017 and 2016, respectively related to Baxalta's funding of the INSPIRE trial. The funding from Baxalta terminated effective August 30, 2016. We have overall responsibility for the trial, including determination of the trial specifications, selection of third party service providers and payment for all services and materials.

Pint International SA

In March 2018, we entered into a License, Development and Commercialization Agreement (the "License Agreement") with Pint International SA (which, together with its affiliate Pint Pharma GmbH, are collectively referred to as "Pint"). Under the terms of the License Agreement, we granted Pint an exclusive, royalty-bearing license, with the right to sublicense, under certain Company patent rights and know-how to develop and commercialize any pharmaceutical product (the "Product") containing rigosertib in all uses of rigosertib or the Product in humans (the "Field") in Latin America countries (the "Territory," including Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, French Guiana, British Guiana, Suriname, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay and Venezuela). We retain the right to develop and commercialize pharmaceutical products containing rigosertib worldwide except for the sale of the Product in the Field in the Territory.

Pint has agreed to make an upfront equity investment and a subsequent equity investment in our common stock. In addition, we could receive up to $42.75 million in additional regulatory, development and sales-based milestone payments as well as tiered, double digit royalties based on net aggregate net sales in the Territory. Pint also has agreed to purchase rigosertib and the Product exclusively from us in accordance with a supply and quality agreement between the parties.

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Pint may terminate the License Agreement in whole (but not in part) at any time upon 45 days' prior written notice. The License Agreement also contains customary provisions for termination by either party in the event of breach of the License Agreement by the other party, subject to a cure period, or bankruptcy of the other party.

Preclinical Collaboration

HanX Biopharmaceuticals, Inc.

In December 2017, we entered into a license and collaboration agreement with HanX Biopharmaceuticals, Inc. ("HanX"), a company focused on development of novel oncology products, for the further development, registration and commercialization in China of ON 123300. This compound has the potential to overcome the limitations of current generation CDK 4/6 inhibitors. Under the terms of the agreement, we will receive an upfront payment, regulatory and commercial milestone payments, as well as royalties on Chinese sales. The key feature of the collaboration is that HanX will provide all funding required for Chinese IND enabling studies performed for Chinese Food and Drug Administration IND approval. We and HanX also intend for these studies to comply with the FDA standards. Accordingly, such studies may be used by us for an IND filing with the FDA. We and HanX will oversee the IND enabling studies. We will maintain global rights outside of China.

GBO, LLC

In December 2012, we entered into an agreement with GVK Biosciences Private Limited, or GVK, to form GBO, LLC, or GBO, a joint venture entity owned by us and GVK. During 2013, GVK made an initial capital contribution of $500,000 in exchange for a 10% interest in GBO, and we contributed a sublicense to the intellectual property related to two of our preclinical programs in exchange for a 90% interest. In November 2014, GVK made a second capital contribution of $500,000 which increased its interest in GBO to 17.5% (and decreased our interest to 82.5%). The two preclinical programs sublicensed to GBO have not been developed to clinical stage as we had initially hoped, and we are in discussions with GVK regarding the future of GBO.

Intellectual Property

Patents and Proprietary Rights

Our intellectual property is derived through our internal research, licensing agreements with Temple University, or Temple, and licensing research agreements with the Mount Sinai School of Medicine, or Mount Sinai.

License Agreement with Temple University

In January 1999, we entered into a license agreement with Temple as subsequently amended, to obtain an exclusive, world-wide license to certain Temple patents and technical information to make, have made, use, sell, offer for sale and import several classes of novel compounds, including our three clinical-stage product candidates, rigosertib, briciclib and recilisib.

Under the terms of the license agreement, we paid Temple a non-refundable up-front payment, and are required to pay annual license maintenance fees, as well as a low single-digit percentage of net sales as a royalty. In addition, we agreed to pay Temple 25% of any consideration received from any sublicensee of the licensed Temple patents and technical information, which does not include any royalties on sales, funds received for research and development or proceeds from any equity or debt investment.

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The license agreement with Temple can be terminated by mutual agreement or due to the material breach or bankruptcy of either party. We may terminate the license agreement for any reason by giving Temple prior written notice.

Research Agreement with Mount Sinai School of Medicine

In May 2010, we entered into a research agreement with Mount Sinai. This agreement is described in more detail under the caption "Certain Relationships and Related Party Transactions Research Agreement."

Rigosertib Patents

As of March 2018, we owned or exclusively licensed 85 issued patents and 12 pending patent applications covering composition-of-matter, process, formulation and various indications for method-of-use for rigosertib filed worldwide, including seven patents and two patent applications in the United States. The U.S. composition-of-matter patent for rigosertib, which we in-licensed pursuant to the license agreement with Temple, currently expires in 2026. The U.S. method of treatment patent for rigosertib, which we also in-licensed from Temple, expires in 2025. A patent covering the use of rigosertib in combination with anticancer agents including azacitidine is issued and will expire in 2028. Patent term extensions may be available, depending on various provisions in the law.

Briciclib Patents

As of March 2018, we owned or exclusively licensed 28 issued patents and one pending patent application covering composition-of-matter, process, formulation and various indications for method-of-use for briciclib filed worldwide, including one patent in the United States. The U.S. composition-of-matter patent for briciclib expires in 2025.

Recilisib Patents

As of March 2018, we owned or exclusively licensed 62 issued patents and three pending patent applications covering composition of matter, formulation and various indications for method-of-use for recilisib filed worldwide, including six patents in the United States. The U.S. composition-of-matter patent for recilisib expires in 2020 and the U.S. formulation patent expires in 2031.

General Considerations

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify a proprietary position for our product candidates will depend upon our success in obtaining effective patent claims and enforcing those claims once granted.

Our commercial success will depend in part upon not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our product candidates or processes, obtain licenses or cease certain activities. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. If a third party commences a patent infringement action against us, or our collaborators, it could consume significant financial and management resources, regardless of the merit of the claims or the outcome of the litigation.

The term of a patent that covers an FDA-approved drug may be eligible for additional patent term extension, which provides patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under

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regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

Furthermore, we may be able to obtain extension of patent term by adjustment of the said term under the provisions of 35 U.S.C. § 154 if the issue of an original patent is delayed due to the failure of the U.S. Patent and Trademark Office. For example, we have received adjustments of 1,139 days extension to the patent term for the rigosertib composition of matter patent (US 7,598,232), 1,155 days extension for the patent covering the process for making rigosertib (US 8,143,453) and 751 days extension for rigosertib formulation patent (US 8,063,109) under the provisions of 35 U.S.C. §154.

We have received orphan designation for rigosertib for the treatment of MDS in the US and Europe. Our partner SymBio has received similar designation in Japan.

In addition to patents, we rely upon unpatented trade secrets, know-how and continuing technological innovation to develop and maintain a competitive position. We seek to protect our proprietary information, in part, through confidentiality agreements with our employees, collaborators, contractors and consultants, and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants and collaborators. 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 a relationship with a third party.

Competition

The pharmaceutical industry is highly competitive and subject to rapid and significant technological change. While we believe that our development experience and scientific knowledge provide us with competitive advantages, we face competition from both large and small pharmaceutical and biotechnology companies. There are a number of pharmaceutical companies, biotechnology companies, public and private universities and research organizations actively engaged in the research and development of products that may compete with our products. Many of these companies are multinational pharmaceutical or biotechnology organizations, which are pursuing the development of, or are currently marketing, pharmaceuticals that target the key oncology indications or cellular pathways on which we are focused.

It is probable that the increasing incidence and prevalence of cancer will lead to many more companies seeking to develop products and therapies for the treatment of unmet needs in oncology. Many of our competitors have significantly greater financial, technical and human resources than we have. Many of our competitors also have a significant advantage with respect to experience in the discovery and development of product candidates, as well as obtaining FDA and other regulatory approvals of products and the commercialization of those products. We anticipate intense and increasing competition as new drugs enter the market and as more advanced technologies become available. Our success will be based in part on our ability to identify, develop and manage a portfolio of drugs that are safer and more effective than competing products in the treatment of cancer patients.

Myelodysplastic Syndromes

There are several ongoing clinical trials aimed at expanding the use of approved chemotherapeutic and immunomodulatory agents in higher-risk MDS, as well as several new clinical programs testing novel technologies in this area. Companies competing in this space include Eisai Inc. (decitabine), Celgene Corporation (azacitidine in combination with lenalidomide, Cell Therapeutics, Inc. (tosedostat

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in combination with decitabine or cytarabine), Cyclacel Pharmaceuticals, Inc. (sapacitabine), Astex/Otsuka (guadecitabine) and Agios Pharmaceuticals, Inc. (enasidenib and ivosidenib). To our knowledge, there are no Phase 3 trials being conducted for higher-risk MDS patients who have failed treatment with HMAs. In the lower-risk MDS market, we face competition from a number of companies in mid-stage and late-stage clinical trials, such as Celgene Corporation (lenalidomide), Array BioPharma Inc (ARRY-614), and Acceleron Pharma (sotatercept and luspatercept).

Acute Radiation Syndrome

Competitors developing products to address ARS include Soligenix, Inc., Cellerant Therapeutics, Inc., and Cleveland BioLabs, Inc. Each of these companies is working with the U.S. government to develop its products through federal contracts and grants.

Manufacturing

Our product candidates are synthetic small molecules. Manufacturing activities must comply with FDA current good manufacturing practices, or cGMP, regulations. We conduct our manufacturing activities under individual purchase orders with third-party contract manufacturers ("CMOs"). We have quality agreements in place with our key CMOs. We have also established an internal quality management organization, which audits and qualifies CMOs in the United States and abroad.

We are working with CMOs to produce the rigosertib active pharmaceutical ingredient, which we believe will enable us to launch and commercialize rigosertib IV if and when marketing approval is obtained. Other CMOs produce rigosertib IV and rigosertib oral for use in our clinical trials. We believe that the manufacturing processes for the active pharmaceutical ingredient and finished drug products for rigosertib are being developed to adequately support future development and commercial demands.

The FDA regulates and inspects equipment, facilities and processes used in manufacturing pharmaceutical products prior to approval. If we fail to comply with applicable cGMP requirements and conditions of product approval, the FDA may seek sanctions, including fines, civil penalties, injunctions, suspension of manufacturing operations, operating restrictions, withdrawal of FDA approval, refusal to approve applications, seizure or recall of products and criminal prosecution. Although we periodically monitor the FDA compliance of our third-party CMOs, we cannot be certain that our present or future third-party CMOs will consistently comply with cGMP and other applicable FDA regulatory requirements.

Commercial Operations

We do not currently have an organization for the sales, marketing and distribution of pharmaceutical products. We may rely on licensing and co-promotion agreements with strategic partners for the commercialization of our products in the United States and other territories. If we choose to build a commercial infrastructure to support marketing in the United States, such commercial infrastructure could be expected to include a targeted, oncology sales force supported by sales management, internal sales support, an internal marketing group and distribution support. To develop the appropriate commercial infrastructure internally, we would have to invest significant financial and management resources, some of which would have to be deployed prior to any confirmation that rigosertib will be approved.

Government Regulation

As a pharmaceutical company that operates in the United States, we are subject to extensive regulation by the FDA, and other federal, state, and local regulatory agencies. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and its implementing regulations set forth, among other things,

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requirements for the research, testing, development, manufacture, quality control, safety, effectiveness, approval, labeling, storage, record keeping, reporting, distribution, import, export, advertising, marketing, and promotion of our products. Although the discussion below focuses on regulation in the United States, we anticipate seeking approval for, and marketing of, our products in other countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of approval and regulation in Europe are addressed in a centralized way through the EMA, but country-specific regulation remains essential in many respects and enforcement is generally through EU member state authorities. The process of obtaining regulatory marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and may not be successful. In addition, approval in the United States does not automatically result in approval in the European Union or elsewhere.

United States Government Regulation

The FDA is the main regulatory body that controls pharmaceuticals in the United States, and its regulatory authority is based in the FDC Act. Pharmaceutical products are also subject to other federal, state and local statutes. A failure to comply explicitly with any requirements during the product development, approval, or post-approval periods, may lead to administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an institutional review board, or IRB, or Independent Ethics Committee (IEC) of a hold on clinical trials, refusal to approve pending marketing applications or supplements, withdrawal of approval, warning letters, untitled letters, cyber letters, product recalls, product seizures or detention, prohibition on importing or exporting, total or partial suspension of production or distribution, injunctions, fines, civil penalties, adverse publicity, disgorgement, restitution, FDA debarment, debarment from government contracting or refusal of future orders under existing contracts, exclusion from Federal healthcare programs, corporate integrity agreements, consent decrees, or criminal prosecution.

The steps required before a new drug may be marketed in the United States generally include:

Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's GLP regulations;

Submission to the FDA of an IND to support human clinical testing;

Approval by an IRB at each clinical site or centrally before each trial may be initiated;

Performance of adequate and well-controlled clinical trials in accordance with federal regulations and with current good clinical practices, or GCPs, to establish the safety and efficacy of the investigational drug product for each targeted indication;

Submission of a new drug application ("NDA") to the FDA;

Satisfactory completion of an FDA Advisory Committee review, if applicable;

Satisfactory completion of an FDA inspection of the manufacturing facilities at which the investigational product is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate, as well as satisfactory completion of FDA inspections of selected clinical trial sites to ensure that clinical trials were conducted in accordance with GCPs; and

FDA review and approval of the NDA.

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Preclinical and Clinical Trials

The testing and approval process of product candidates requires substantial time, effort, and financial resources. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease. Product development typically begins with preclinical studies. Preclinical studies include laboratory evaluation of chemistry, pharmacology, toxicity, and product formulation, as well as animal studies to assess potential safety and efficacy. Such studies must generally be conducted in accordance with the FDA's GLPs.

Prior to commencing the first clinical trial with a product candidate, an IND sponsor must submit the results of the preclinical tests and preclinical literature, together with manufacturing information, analytical data, any available clinical data or literature, and proposed clinical study protocols among other things, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. This authorization is required before interstate shipping and administration of any new drug product to humans that is not the subject of an approved NDA. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational drug to patients under the supervision of qualified investigators following GCPs, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors. Clinical trials are conducted under protocols that detail the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND. The informed written consent of each participating subject is required. The clinical investigation of an investigational drug is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

Phase 1. Phase 1 includes the initial introduction of an investigation drug into humans. Phase 1 clinical trials may be conducted in patients with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, metabolism, pharmacokinetics and pharmacologic actions of the investigational drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1 clinical trials, sufficient information about the investigational product's pharmacokinetics and pharmacological effects may be obtained to permit the design of Phase 2 clinical trials. The total number of participants included in Phase 1 clinical trials varies, but is generally in the range of 20 to 80.

Phase 2. Phase 2 includes the controlled clinical trials conducted to evaluate the effectiveness of the investigational product for a particular indication(s) in patients with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the drug. Phase 2 clinical trials are typically well-controlled, closely monitored, and conducted in a limited patient population, usually involving no more than several hundred participants.

Phase 3. Phase 3 clinical trials are controlled clinical trials conducted in an expanded patient population at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the investigational product has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the product, and to provide an adequate basis for product approval. Phase 3 clinical trials usually involve several hundred to several thousand participants. In most cases, the FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate

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the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Certain study designs may lend themselves more to such reliance. However, even if a study meets these criteria, a single study may not be sufficient if there is a possibility of an incorrect outcome. All available data must further be examined for their potential to either support or undercut reliance on a single trial.

In addition to the above traditional kinds of data required for the approval of an NDA, the recently passed 21st Century Cures Act provides for FDA acceptance of new kinds of data such as patient experience data, real world evidence for already approved products, and, for appropriate indications sought through supplemental marketing applications, data summaries.

The decision to terminate development of an investigational drug product may be made by either a health authority body, such as the FDA or IRB/independent ethics committees ("IECs"), or by a company for various reasons. An IRB approves the initiation of a clinical trial and supervises the conduct of the trial to ensure that the risks to human subjects are reasonable in relation to the anticipated benefits and that there are adequate human subject protections in place. The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. In some cases, clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor, or the clinical monitoring board. This group provides guidance on whether or not a trial may or should move forward at designated check points. These decisions are based on the limited access to data from the ongoing trial. The suspension or termination of development can occur during any phase of clinical trials if it is determined that the participants or patients are being exposed to an unacceptable health risk, if the product candidate does not show sufficient evidence of efficacy, if the development program does not comply with applicable regulatory requirements, or due to changing sponsor business objectives.

In addition, there are various reporting requirements that clinical trial sponsors and investigators must comply with during the course of a clinical trial. For instance, there are requirements for the registration of ongoing clinical trials of drugs on public registries and the disclosure of certain information pertaining to the trials as well as clinical trial results after completion. Sponsors must also make annual reports to FDA concerning the progress of their clinical trial programs as well as more frequent reports for certain serious adverse events. Sponsors must submit a protocol for each clinical trial, and any subsequent protocol amendments to FDA and the applicable IRBs. IRBs must also receive information concerning unanticipated problems involving risks to subjects. Investigators must further provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA. Moreover, under the 21st Century Cures Act, manufacturers or distributors of investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions must have a publicly available policy concerning expanded access to investigational drugs.

Further, the manufacture of investigational drugs for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational drug products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDC Act.

A sponsor may be able to request a special protocol assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will

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form the primary basis of an efficacy claim, as well as preclinical carcinogenicity trials and stability studies. A sponsor meeting the regulatory criteria may make a specific request for a SPA and provide FDA with a copy of the proposed protocol as well as other information regarding the design and size of the proposed clinical trial. A SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins. If a written agreement is reached, it will be documented and made part of the record. The agreement will be binding on the FDA and may not be changed by the sponsor or the FDA after the trial begins except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the product candidate was identified after the testing began. A SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to a SPA. Having a SPA agreement does not guarantee that a product will receive FDA approval.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate 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 product candidate and, among other things, must develop methods for testing the identity, strength, quality, potency, and purity of the final product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational drug product information is submitted to the FDA in the form of a NDA to request market approval for the product in specified indications.

New Drug Applications

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the drug product for the proposed indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product to the satisfaction of the FDA.

In most cases, the NDA must be accompanied by a substantial user fee (currently exceeding $2,421,000); there may be some instances in which the user fee is waived. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. After the NDA submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. For new molecular entities, or NMEs, FDA has the goal of completing its review within ten months of the application's acceptance for filing. This, however, is just a goal, and the review time may take longer. For instance, the FDA can extend this review by three months to consider certain late-submitted information or information intended to clarify information already provided in the submission. The FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP. The FDA may refer applications for novel drug products which present difficult questions of safety or efficacy to an advisory committee, typically a

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panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. For drugs for which no active ingredient (including any ester or salt of active ingredients) has previously been approved by the FDA, the FDA must refer the drug to an advisory committee or provide in an action letter, a summary of the reasons why the FDA did not refer the product candidate to an advisory committee. Product candidates may also be referred to advisory committees for other reasons. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product 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. After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter indicates that the review cycle of the application is complete and the application is not ready for approval. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application, including additional clinical trials. If a complete response letter is issued, the applicant may either: resubmit the NDA, addressing all of the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. If, or 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. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can 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 requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing, clinical trials, and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs, including the imposition of user fees for certain supplements.

Advertising and Promotion

The FDA and other federal regulatory agencies closely regulate the marketing and promotion of drugs through, 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. A product cannot be commercially promoted before it is approved. After approval, product promotion can include only those claims relating to safety and

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effectiveness that are consistent with the labeling approved by the FDA. Healthcare providers are permitted to prescribe drugs for "off-label" uses that is, uses not approved by the FDA and therefore not described in the drug's labeling because the FDA does not regulate the practice of medicine. However, FDA regulations impose stringent restrictions on manufacturers' communications regarding off-label uses. Broadly speaking, a manufacturer may not promote a drug for off-label use, but may engage in non-promotional, balanced communication regarding off-label use under specified conditions. Failure to comply with applicable FDA requirements and restrictions in this area may subject a company to adverse publicity and enforcement action by the FDA, the Department of Justice (the "DOJ"), or the Office of the Inspector General of the Department of Health and Human Services ("HHS"), 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.

Post-Approval Regulations

After regulatory approval of a drug is obtained, a company is required to comply with a number of post-approval requirements. For example, as a condition of approval of an NDA, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug. In addition, as a holder of an approved NDA, a company would be required to report adverse reactions and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of its products. Further, under the Drug Quality and Security Act, manufacturers have obligations concerning the tracking and tracing of drug products, as well as the investigation and reporting of suspect and illegitimate products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval to assure and preserve the long term stability of the drug or biological product. Manufacturing facilities must be registered with FDA and marketed drug products must be listed. Sponsors are also subject to annual program fees. These facilities and products are subject to annual user fees, though there may be some exemptions. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural and substantive record keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may 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 a company and any third-party manufacturers that a company may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, such as risk evaluation and mitigation strategies and phase 4 studies. Also, new government requirements, including those resulting from new

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legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development or result in additional post-approval requirements.

After a product is approved for commercial sale, in addition to marketing and promotion restrictions, manufacturers are subject to federal and state laws and regulations requiring them to report certain pricing data, transactions with medical professionals, and similar information. Manufacturers participating in federal health care programs are also required to provide statutorily mandated discounts and rebates.

FDA Animal Efficacy Rule for Approval of Medical Countermeasures

Marketing approval by the FDA for new medical countermeasures in situations for which human efficacy testing is not feasible or ethical, such as for ARS, is based on the so-called "Animal Efficacy Rule." Under this rule, FDA can rely on the evidence from adequate and well-controlled animal studies to provide substantial prediction of effectiveness of an agent in humans, when coupled with:

- a reasonably well understood pathophysiological mechanism for the toxicity of the radiological or nuclear substance and its amelioration or prevention by the agent;
- protective effect is demonstrated in generally more than one animal species expected to react with a response predictive for humans, and hence be a reliable indicator of its effectiveness in humans;
- animal study endpoint is clearly related to the desired benefit in humans; and
- data or information on the pharmacokinetics and pharmacodynamics, and other relevant data or information, of the product in animals and humans is sufficiently well understood to allow selection of a dose predicted to be effective in humans.

Drug safety under the animal rule, however, must be evaluated under existing requirements for establishing the safety of new drugs. Drugs approved under the animal rule are subject to the following elevated post-approval requirements:

- applicants must conduct post-marketing studies to verify and describe the drug's clinical benefit and to assess safety when such studies are feasible and ethical. To these ends, applicants must include a plan or approach in their NDA to such a study in the event they become ethical and feasible;
- if FDA finds that a drug approved under the animal rule can be safely used only if distribution or use is restricted, FDA will require post-marketing restrictions commensurate with the safety concerns presented by the drug; and
- the product's patient labeling must explain that for ethical or feasibility reasons, the drug's approval was based on animal studies alone.

Sponsors of drugs approved under the animal rule also must submit promotional materials to FDA prior to dissemination.

Approvals based on the animal rule may be withdrawn for a variety of reasons, including a post-marketing study's failure to verify clinical benefit, an applicant's failure to perform the post-marketing study with due diligence, and a finding that post-marketing restrictions are inadequate to ensure safe use.

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The Hatch-Waxman Amendments to the FDC Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product or method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA or 505(b)(2) application. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, pre-clinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. 505(b)(2) applications provide for marketing of a drug product that may have the same active ingredients as the listed drug and contain the same full safety and effectiveness data as an NDA, but at least some of the information comes from studies not conducted by or for the applicant. 505(b)(2) applicants may rely on published literature or FDA's prior finding of safety and effectiveness for an NDA approved drug product. The ANDA or 505(b)(2) applicant is required to certify to the FDA concerning any patents listed for the approved product referenced in the marketing application in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA or 505(b)(2) applicant may also elect to submit a statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge or carve out the listed patents, the ANDA or 505(b)(2) application approval will not be made effective until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA or 505(b)(2) 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 or 505(b)(2) application has been accepted for filing by the FDA and no later than 20 days following the applicant's receipt of FDA's Paragraph IV acknowledgement letter. 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 of the receipt of a Paragraph IV certification automatically prevents the FDA from making an approval of the ANDA or 505(b)(2) application effective until the earlier of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant, or such shorter or longer period as may be determined by a court.

The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Exclusivity

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which the FDA cannot receive any ANDA seeking approval of a generic

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version of that drug or a 505(b)(2) application citing that drug as a reference listed drug. Certain changes to a drug, such as the addition of a new indication to the package insert, may be associated with a three-year period of exclusivity during which the FDA cannot approve an ANDA for a generic drug or a 505(b)(2) application that includes the change, if the applicant conducted clinical trials essential to the approval of the application, which are not bioavailability or bioequivalence studies. Such exclusivity in the EU under a broadly equivalent regime is ten years.

An ANDA or a 505(b)(2) application may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA or a 505(b)(2) application which references an approved NCE may be filed before the expiration of the exclusivity period.

Patent Term Extension

After NDA approval, owners of relevant drug patents may apply for up to a five year patent extension of a single unexpired patent, that has not previously been extended. The allowable patent term extension is calculated as half of the drug's testing phase the time between IND application and NDA submission and all of the review phase the time between NDA submission and approval up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years from the date of approval. Similar extension rules apply in the EU.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act ("FCPA"), prohibits any U.S. individual or business from paying, offering, or 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 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.

Europe and Other International Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Some countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical trials. In Europe, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee (IEC), much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

To obtain regulatory approval to commercialize a new drug under European Union regulatory systems, we must submit a marketing authorization application, or MAA. The MAA is similar to the NDA, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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Compliance

During all phases of development (pre- and post-marketing), failure to comply with applicable regulatory requirements may result in administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an institutional review board, or IRB, of a hold on clinical trials, refusal to approve pending marketing applications or supplements, withdrawal of approval, warning letters, untitled letters, cyber letters, product recalls, product seizures or detention, prohibition on importing or exporting, total or partial suspension of production or distribution, injunctions, fines, civil penalties, adverse publicity, disgorgement, restitution, FDA debarment, debarment from government contracting or refusal of future orders under existing contracts, exclusion from Federal healthcare programs, corporate integrity agreements, consent decrees, or criminal prosecution, FDA's imposition of a clinical hold on trials, refusal to approve pending applications, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

Other Special Regulatory Procedures

Orphan Drug Designation

The FDA may grant Orphan Drug Designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or, if the disease or condition affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making the drug would be recovered from sales in the United States. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan designation if there is a product already approved by the FDA that is intended for the same indication and that is considered by the FDA to be the same as the already approved product. This hypothesis must be demonstrated to obtain orphan exclusivity. In the European Union, the EMA's Committee for Orphan Medicinal Products, or COMP, grants Orphan Drug Designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life- threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug.

In the United States, Orphan Drug Designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs for certain kinds of studies, tax credits for certain research and user fee waivers under certain circumstances. Under the recently passed 21st Century Cures Act, Congress expanded the potential opportunities for grant funding to include additional kinds of studies. The 2017 Tax Cuts and Jobs Act, however, reduced the available tax credits for orphan products. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to seven years of market exclusivity, which means the FDA may not approve any other application for the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

In the European Union, Orphan Drug Designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following drug approval. This period may be reduced to six years if the Orphan Drug Designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify

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maintenance of market exclusivity or where the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product,. As with the FDA, orphan drug exclusivity does not prevent the EMA from approving a second medicinal product where such the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

Orphan drug designation must be requested before submission of an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of the regulatory review and approval process.

Priority Review (United States), Accelerated Review (European Union) and other Expedited Programs

The FDA has various programs, including Fast Track designation, accelerated approval, priority review and breakthrough designation, that are intended to expedite or simplify the process for the development and FDA review of certain drug products that are intended for the treatment of serious or life threatening diseases or conditions, and demonstrate the potential to address unmet medical needs or present a significant improvement over existing therapy. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a Fast Track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if the product will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy, safety, or public health factors. If Fast Track designation is obtained, drug sponsors may be eligible for more frequent development meetings and correspondence with the FDA. In addition, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information.

Based on results of one or more Phase 3 clinical trials submitted in an NDA, upon the request of an applicant, a priority review designation may be granted to a product by the FDA, which sets the target date for FDA action on the application at six months from FDA filing, or eight months from the sponsor's submission. Priority review is given to drugs intended to treat serious conditions and which, if approved would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of the serious condition. If criteria are not met for priority review, the standard FDA review period is ten months from FDA filing, or 12 months from sponsor submission. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, 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 drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are eligible for the Fast Track designation features as described above, intensive guidance on an efficient drug development program beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review.

In addition, products for treating serious or life threatening conditions and that provide a meaningful advantage over available therapies may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical

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endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, FDA will require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoints. The drug may be subject to accelerated withdrawal procedures if such studies do not verify the product's clinical benefit or other evidence shows a lack of safety or efficacy. Promotional materials for products approved via the accelerated approval pathway must be submitted to FDA prior to initial distribution. Such products may also be subject to distribution or use restrictions, if FDA determines that restrictions are needed to assure safe use. We are in discussions with the FDA concerning the development pathway for our combination product candidate.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Under the Centralized Procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the EMA's Committee for Medicinal Products of Human Use, or CHMP)). On average, an approval is provided by the European Commission after approximately 15 months. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease (e.g., heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days. There is also a conditional marketing authorization which allows for the early approval of a medicine on the basis of less complete clinical data than normally required, if the medicine addresses an unmet medical need and targets a seriously debilitating or life-threatening disease, a rare disease or is intended for use in emergency situations in response to a public health threat. The benefit to public health must outweigh the risk due to the limited availability of clinical data at the time of marketing authorization.

The EMA has recently been conducting a pilot on 'adaptive pathways' an iterative process building on existing regulatory processes involving gathering evidence through real-life use to supplement clinical trial data.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or certain supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Also, under the FDA Reauthorization Act of 2017, beginning in 2020, sponsors submitting applications for product candidates intended for the treatment of adult cancer which are directed at molecular targets that the FDA determines to be substantially relevant to the growth or progression of pediatric cancer must submit, with the application, reports from molecularly targeted pediatric cancer investigations designed to yield clinically meaningful pediatric study data, using appropriate formulations, to inform potential pediatric labeling. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted.

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity patent or non-patent for a drug if certain conditions are met. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in

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the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the required timeframe. 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. This is not a patent term extension, but it effectively extends the regulatory exclusivity period. Moreover, pediatric exclusivity attaches to all formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety as that which was studied. Applications under the BPCA for labeling changes receive priority review designation, with all of the benefits that designation confers.

In the European Union all applications for marketing authorization for new medicines have to include the results of studies as described in an agreed pediatric investigation plan, unless the medicine receives a deferral or waiver. Medicines authorized across the EU with the results of studies from a pediatric investigation plan included in the product information are eligible for an extension of their supplementary protection certificate by six months. This is the case even when the studies' results are negative. For orphan medicines, the incentive is an additional two years of market exclusivity.

Different pricing and reimbursement schemes exist in other countries. In the European Union, national governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very 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 a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements of our products.

Healthcare Reform

Enacted in 2010, the President of the United States signed into law the Patient Protection and Affordable Care Act, or which we refer to collectively as the Affordable Care Act. The Affordable Care Act substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. The Affordable Care Act is a sweeping law intended to, by broadening access to health insurance, reduce or constrain the growth of healthcare spending, enhance enhancing remedies against fraud and abuse, adding new transparency requirements for healthcare and health insurance industries, impose imposing new taxes and fees on the health industry, and impose imposing additional health policy reforms intended to reduce or constrain the growth of healthcare spending.

Among the Affordable Care Act's provisions of importance to the pharmaceutical industry are the following:

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 some government healthcare programs;

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23% and 13% of the average manufacturer price for most branded and generic drugs, respectively;

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

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

extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;

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

new requirements to report annually specified financial arrangements with physicians and teaching hospitals, as defined in the Affordable Care Act and its implementing regulations, including reporting any "payments or transfers of value" made or distributed to prescribers, teaching hospitals, and other healthcare providers and reporting any ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection required beginning August 1, 2013 and reporting to the Centers for Medicare and Medicaid Services required by March 31, 2014 and by the 90th day of each subsequent calendar year;

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

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

a mandatory nondeductible payment for employers with 50 or more full time employees (or equivalents) who fail to provide certain minimum health insurance coverage for such employees and their dependents, beginning in 2015 (pursuant to relief enacted by the Treasury Department).

The Affordable Care Act also established an Independent Payment Advisory Board, or IPAB, to reduce the per capita rate of growth in Medicare spending. Beginning in 2014, IPAB was mandated to propose changes in Medicare payments if it determines that the rate of growth of Medicare expenditures exceeds target growth rates. The IPAB has broad discretion to propose policies to reduce expenditures, which may have a negative impact on payment rates for pharmaceutical products. A proposal made by the IPAB is required to be implemented by the U.S. government's Centers for Medicare & Medicaid Services, or CMS, unless Congress adopts a proposal with savings greater than those proposed by the IPAB. IPAB proposals may impact payments for physician and free-standing services beginning in 2015 and for hospital services beginning in 2020. Recently, CMS finalized a rule that reduces the Medicare Part B payment to certain hospitals for outpatient drugs the hospitals purchase at a statutory discount under the 340B Program. This regulation may impact acquisition of drugs administered by physicians in hospital outpatient departments and clinics.

In addition, other legislative changes have been adopted since the Affordable Care Act was enacted. On August 2, 2011, the President signed into law The Budget Control Act of 2011, which,

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among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. On January 2, 2013, President Obama signed into law The American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several 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, which could have a material adverse effect on our customers and accordingly, our financial operations. The Bipartisan Budget Act of 2018 increased manufacturer liability for Medicare Part D covered prescriptions in the period of the coverage gap.

The Affordable Care Act was amended by the Tax Cuts and Jobs Act of 2017 to repeal the individual penalty for not purchasing health insurance, and it may be further repealed and replaced by Congress. Changes in the law may result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition, and results of operations.

Coverage and Reimbursement

In the US, many independent third-party payers, as well as the Medicare and state Medicaid programs, reimburse buyers of pharmaceutical products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the federal program administered by the states to provide health care benefits to certain indigent persons. In return for including our pharmaceutical commercial products in the Medicare and Medicaid programs, we may need to agree to calculate and report certain price points to the Centers for Medicare and Medicaid Services, and pay a rebate to state Medicaid agencies that provide reimbursement for those products in an outpatient setting. We will also have to agree to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service, and the Indian Health Service, as well as certain hospitals, community health centers, clinics, and other providers that are designated as 340B covered entities (entities designated by federal programs statute to receive mandatory drug discounts under the 340B program drugs at discounted prices) at prices that are significantly below the price we may charge to commercial pharmaceutical distributors. These programs and contracts are highly regulated and may impose restrictions on our business, including penalties for price increases that exceed the rate of inflation. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue selling our drugs to the federal government or receiving reimbursement for our drugs once approved.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become

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very 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 a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for dug products will allow favorable reimbursement and pricing arrangements of our products.

Other Healthcare Laws and Compliance Requirements

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some business arrangements from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from federal Anti-Kickback Statute liability. The reach of the Anti-Kickback Statute was broadened by the Affordable Care Act, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal civil False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the U.S. government. The civil False Claims Act authorizes imposition of treble damages and a civil penalty for each false claim submitted, which, for pharmaceutical products, have frequently resulted in multi-million dollar penalties. For violations after November 2, 2015, the penalty has increased from a minimum of $5,500 to $10,781 and a maximum $11,000 to $21,563 for each claim. A civil penalty may be imposed on each invoice or claim for payment and thus potential liability may aggregate into millions of dollars. Pharmaceutical and other healthcare companies have been sued under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been sued for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses, and for reporting false pricing information used to determine discounts, rebates and reimbursement rates. Liability may be predicated on non-compliance with federal laws and regulations under an implied certification theory; however, the Supreme Court has limited liability under this theory by requiring the regulatory violation be material to the government's payment decision. Claims under the civil False Claims Act may be brought by the government or private parties on behalf of the government, called "qui tam" actions, which may proceed even if the government does not join as a party.

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HIPAA created new federal criminal statutes that prohibits, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. The Affordable Care Act amended the intent requirement of certain of these criminal statutes under HIPAA so that a person or entity no longer needs to have actual knowledge of the statute, or the specific intent to violate it, to have committed a violation. Further, the government may prosecute conduct constituting a false claim under the criminal False Claims Act. The criminal False Claims Act prohibits the making or presenting of a claim to the government knowing such claim to be false, fictitious, or fraudulent and, unlike the civil False Claims Act, requires proof of intent to submit a false claim. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

The Affordable Care Act further created new federal requirements for reporting, by applicable manufacturers of covered drugs, payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by HITECH, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates" independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. In addition more onerous foreign data privacy provisions may apply. For instance the forthcoming (25 May 2018) EU General Data Protection Regulation imposes stricter rules on the processing of personal data than apply in the USA and its provisions exclude the export of data relating to identifiable individuals to most countries, including the US, unless certain safeguards are in place.

In the United States, our activities are potentially subject to additional regulation by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare and Medicaid Services, other divisions of HHS (e.g., the Office of Inspector General), the DOJ and individual U.S. Attorney offices within the DOJ, and state and local governments. If a drug product is reimbursed by Medicare or Medicaid, pricing and rebate programs must comply with, as applicable, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 as well as the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990, or the OBRA, and the Veterans Health Care Act of 1992, each as amended. Among other things, the OBRA requires drug manufacturers to pay rebates on prescription drugs to state Medicaid programs and empowers states to negotiate supplemental rebates on pharmaceutical prices, which may result in prices for our future products that will likely be lower than the prices we might otherwise obtain. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Under the Veterans Health Care Act, or VHCA, drug companies are required to offer some drugs at a reduced price to four federal agencies including the U.S. Department of Veterans Affairs and DoD, the Public Health Service and some private Public

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Health Service designated entities in order to participate in other federal funding programs including Medicaid. Recent legislative changes require that these discounted prices are also required to be offered for specified DoD purchases for its TRICARE program via a rebate system. Participation under the VHCA requires submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulation.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private "qui tam" actions brought by individual whistleblowers in the name of the government or refusal to allow us to enter into supply contracts, including government contracts, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in some states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/ or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing specified physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit other specified sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

In Europe, most countries have laws or (more commonly) codes of practice which broadly emulate US 'sunshine laws' and require companies to maintain and publish a record of transfers of value to healthcare professionals. These are in addition to national anti-corruption laws similar to the FCPA for instance the UK Bribery Act 2010 which has a wider scope than the FCPA in many respects including in that it covers relevant decision makers in both the private and public sectors and applies both domestically and internationally.

Employees

As of December 31, 2017, we had 25 employees. We have no collective bargaining agreements with our employees and have not experienced any work stoppages. We believe that our relations with our employees are good.

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Corporate Information

We were incorporated in Delaware in December 1998. Our principal executive offices are located at 375 Pheasant Run, Newtown, PA 18940 and our telephone number is (267) 759-3680. Our website address is www.onconova.com. The information contained in, or that can be accessed through, our website is not part of this report.

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ITEM 1A. ***RISK FACTORS***

You should carefully consider the following risk factors together with the other information contained in this Annual Report, including our financial statements and the related notes appearing in this report. We cannot assure you that any of the events discussed in the risk factors below will not occur. If any of the following risks actually occur, they may materially harm our business and our financial condition and results of operations. In this event, the market price of our securities could decline and your investment could be lost. You should understand that it is not possible to predict or identify all such risks. Consequently, you should not consider the following to be a complete discussion of all potential risks or uncertainties.

Risks Related to Our Financial Position and Capital Needs

We need to obtain additional funding to continue as a going concern; if we are unable to meet our needs for additional funding in the future, we will be required to limit, scale back or cease operations.

Our consolidated financial statements for the year ended December 31, 2017 have been prepared assuming we will continue to operate as a going concern. However, due to our ongoing operating losses and our accumulated deficit, in their opinion on our audited financial statements for our fiscal year ended December 31, 2017, our auditors indicated that there is substantial doubt about our ability to continue as a going concern. Because we continue to experience net operating losses, our ability to continue as a going concern is subject to our ability to successfully raise sufficient additional capital, through future financings or through strategic and collaborative arrangements. If we are unable to obtain additional funding, we may not be able to continue as a going concern.

We do not have the funding resources necessary to carry out all of our proposed operating activities, including our INSPIRE trial. We will need to obtain additional financing in the future in order to fully fund rigosertib or any other product candidates through the regulatory approval process. Accordingly, we may delay or pause our planned clinical trials, including our INSPIRE trial, until we secure adequate additional funding. If we seek to proceed with a clinical trial without additional funding, we may receive questions or comments from the FDA, fail to obtain IRB approval, or find it more difficult to enroll patients in the trial. We have scaled down our operations in order to reduce spending on general and administrative functions, research and development, and other clinical trials, but by themselves, those measures may not be sufficient to address our funding needs.

Our future capital requirements will depend on many factors, including:

- timing and success of our clinical trials for rigosertib;
- continued progress of and increased spending related to our research and development activities;
- conditions in the capital markets and the biopharmaceutical industry, particularly with respect to raising capital or entering into strategic arrangements;
- progress with preclinical experiments and clinical trials, including regulatory approvals necessary for advancement and continuation of our development programs;
- changes in regulatory requirements and guidance of the FDA and other regulatory authorities, which may require additional clinical trials to evaluate safety and/or efficacy, and thus have significant impacts on our timelines, cost projections, and financial requirements;
- ongoing general and administrative expenses related to our reporting obligations under the Securities and Exchange Act of 1934, as amended (the "Exchange Act");
- cost, timing, and results of regulatory reviews and approvals;

costs of any legal proceedings, claims, lawsuits and investigations;

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success, timing, and financial consequences of any existing or future collaborative, licensing and other arrangements that we may establish, including potential granting of licenses to one or more of our programs in various territories, or otherwise monetizing one or more of our programs;

cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;

costs of commercializing any of our other product candidates;

technological and market developments;

compliance with Nasdaq's continued listing requirements;

cost of manufacturing development; and

timing and volume of sales of products for which we obtain marketing approval.

These factors could result in variations from our projected operating and liquidity requirements. Additional funds may not be available when needed, or, if available, we may not be able to obtain such funds on terms acceptable to us. If adequate funds are unavailable, we may be required, among other things, to:

delay, reduce the scope of or eliminate one or more of our research or development programs;

license rights to technologies, product candidates or products at an earlier stage or for indications or territories than otherwise would be desirable, or on terms that are less favorable to us than might otherwise be available;

obtain funds through arrangements that may require us to relinquish rights to product candidates or products that we would otherwise seek to develop or commercialize by ourselves; or

further reduce or cease operations.

We have incurred significant losses since our inception and anticipate that we will continue to incur losses in the future.

We are a clinical-stage biopharmaceutical company. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that a product candidate will fail to gain regulatory approval or become commercially viable. We do not have any products approved by regulatory authorities for marketing and have not generated any revenue from product sales to date, and we continue to incur significant research, development and other expenses related to our ongoing operations. As a result, we are not profitable and have incurred losses in every reporting period since our inception in 1998. For the years ended December 31, 2017, and 2016, we reported net losses of $24.1 million and $19.7 million, respectively, and we had an accumulated deficit of $362.3 million at December 31, 2017.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. These losses may increase as we continue the research and development of, and seek regulatory approvals for, our product candidates, and potentially begin to commercialize any products that may achieve regulatory approval. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues. If any of our product candidates fail in clinical trials or do not gain regulatory approval, or if approved, fail to achieve market acceptance, we may never become profitable. Even if we achieve profitability in the future, we may not be able to sustain

profitability in subsequent periods.

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We currently have no source of product revenue and may never become profitable.

To date, we have not generated any revenues from commercial product sales. Our ability to generate revenue from product sales and achieve profitability will depend upon our ability to successfully commercialize products, including any of our current product candidates, or other product candidates that we may in-license or acquire in the future. Even if we are able to successfully achieve regulatory approval for these product candidates, we do not know when any of these products will generate revenue from product sales for us, if at all. Our ability to generate revenue from product sales from our current or future product candidates also depends on a number of additional factors, including our ability to:

- successfully complete development activities, including the necessary clinical trials;
- complete and submit NDAs, to the U.S. Food and Drug Administration, or FDA, and obtain regulatory approval for indications for which there is a commercial market;
- complete and submit applications to, and obtain regulatory approval from, foreign regulatory authorities;
- successfully complete all required regulatory agency inspections;
- set a commercially viable price for our products;
- obtain commercial quantities of our products at acceptable cost levels;
- develop a commercial organization or contract for a commercial organization capable of sales, marketing and distribution for any products we intend to sell ourselves in the markets in which we choose to commercialize on our own, which will require time and investment in order to train and monitor them with regard to legal compliance, and subjects us to liability for their actions;
- find suitable distribution partners to help us market, sell and distribute our approved products in markets where we decide not to market ourselves; and
- obtain coverage and adequate reimbursement from third parties, including government and private payers.

In addition, because of the numerous risks and uncertainties associated with product development, including that our product candidates may not advance through development or achieve the endpoints of applicable clinical trials, we are unable to predict the timing or amount of increased expenses, or when or if we will be able to achieve or maintain profitability. Even if we are able to complete the development and regulatory process for any product candidates, we anticipate incurring significant costs associated with commercializing these products.

Even if we are able to generate revenues from the sale of our products, we may not become profitable and may need to obtain additional funding to continue operations. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or suspend our operations.

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

Until we can generate substantial revenue from product sales, if ever, we expect to seek additional capital through a combination of private and public equity offerings, debt financings, strategic collaborations and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of existing stockholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the

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rights of existing stockholders. Debt financing, if available, may involve agreements that include restrictive covenants limiting our ability to take important actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic collaborations and alliances or licensing arrangements with third parties, which may include existing collaboration partners, we may have to relinquish valuable rights to our technologies or product candidates, including rigosertib, or grant licenses on terms that are not favorable to us. At December 31, 2017 we had $4.0 million in cash and cash equivalents and in February 2018 we completed an offering of stock and warrants with net proceeds of $8.7 million. Most of this cash will be used to continue our Phase 3 INSPIRE trial and planning for the combination trial; however the cash is insufficient to complete the INSPIRE trial or a Phase 3 combination trial. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates or formulations that we would otherwise prefer to develop and market ourselves.

As of February 28, 2018, we had 18,946,163 shares of common stock issued and outstanding. In addition, as of February 28, 2018, we had no shares of Series A Convertible Preferred Stock issued and outstanding, and 1,044,488 shares of Series A Preferred Stock reserved for issuance upon the exercise of outstanding preferred stock warrants. We intend to hold a special meeting of stockholders on March 21, 2018 to seek stockholders' approval on an amendment to our Tenth Certificate of Incorporation, as amended (the "Certificate of Incorporation") to increase the number of authorized shares of capital stock from 30,000,000 shares to 105,000,000 shares in order to increase the number of authorized shares of common stock from 25,000,000 shares to 100,000,000 shares. On February 28, 2018, we filed with the Securities and Exchange Commission (the "SEC") a definitive proxy statement relating to the special meeting. If the proposed amendment is not approved by our stockholders, (i) our financing alternatives will likely be limited by the lack of sufficient unissued and unreserved authorized shares of common stock, and stockholder value may be harmed by this limitation, and (ii) holders of Series A Convertible Preferred Stock will not be able to convert their shares of Series A Convertible Preferred Stock into common stock, and the value of the Series A Convertible Preferred Stock and preferred stock warrants exercisable into Series A Convertible Preferred Stock may be negatively affected.

Risks Related to Our Business and Industry

Our future success is dependent primarily on the regulatory approval and commercialization of our product candidates, including rigosertib.

We do not have any products that have gained regulatory approval. Currently, our product candidates are rigosertib, briciclib and recilisib, and rigosertib is our only late-stage product candidate.

As a result, our business is substantially dependent on our ability to obtain regulatory approval for, and, if approved, to successfully commercialize rigosertib and, to a lesser degree, briciclib and recilisib in a timely manner. We cannot commercialize product candidates in the United States without first obtaining regulatory approval for the product from the FDA. Similarly, we cannot commercialize product candidates outside of the United States without obtaining regulatory approval from comparable foreign regulatory authorities. Before obtaining regulatory approvals for the commercial sale of any product candidate for a target indication, we must demonstrate with substantial evidence gathered in preclinical and well-controlled clinical studies, generally including two well-controlled Phase 3 trials, and, with respect to approval in the United States, to the satisfaction of the FDA, that the product candidate is safe and effective for use for that target indication and that the manufacturing facilities, processes and controls are adequate. Even if rigosertib or another product candidate were to successfully obtain approval from the FDA and comparable foreign regulatory authorities, any approval might contain significant limitations related to use restrictions including restrictions on acceptable

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populations, such as for specified age groups, warnings, black box warnings, precautions or contraindications, or may be subject to burdensome post-approval study or risk management requirements. The applicable regulatory authorities also may not include information in the approved label for the product necessary for us to make desired claims. If we are unable to obtain regulatory approval for rigosertib 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 of briciclib, recilisib, or any other product candidate that we may discover, in-license, develop or acquire in the future. Furthermore, even if we obtain regulatory approval for rigosertib, we will still need to develop a commercial organization, 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 rigosertib, we may not be able to earn sufficient revenues to continue our business.

The results of preclinical testing or earlier clinical studies are not necessarily predictive of future results. Rigosertib, or any other product candidate we advance into clinical trials may not have favorable results in later-stage clinical trials or receive regulatory approval.

Success in preclinical testing and earlier clinical studies does not ensure that later clinical trials will generate adequate data to demonstrate the efficacy and safety of an investigational drug. A number of companies in the pharmaceutical and biotechnology industries, including those with greater resources and experience, have suffered significant setbacks in clinical trials, even after seeing promising results in earlier clinical trials. Despite the results reported in earlier clinical trials for rigosertib and our other clinical-stage product candidates, we do not know whether the later-stage clinical trials we may conduct in the future will demonstrate adequate efficacy and safety to result in regulatory approval to market any of our product candidates in any particular jurisdiction. For instance, our ONTIME trial did not meet its primary efficacy endpoint. Our other Phase 3 studies also may not meet their primary endpoints or may have safety results that prevent regulatory approval. If this were to occur, the FDA would not approve an NDA, even if positive results are found for a sub-set of the study's population. Moreover, if a study does not meet its primary endpoint, but the result is due to a population sub-set, FDA may not approve an NDA at all or may only approve it for the specific sub-set of patients. If later-stage clinical trials do not produce favorable results, our ability to achieve regulatory approval for any of our product candidates may be adversely impacted.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome.

Clinical testing is expensive, can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and early clinical trials.

We may experience delays in our ongoing or future clinical trials and we do not know whether planned clinical trials will begin or enroll subjects on time, need to be redesigned or be completed on schedule, if at all. For example, in December 2015, the FDA put the briciclib IND on full clinical hold following a drug product lot testing failure. There can be no assurance that the FDA or a comparable foreign regulatory authority will not put clinical trials of any of our product candidates on clinical hold in the future. Clinical trials may be delayed, suspended or prematurely terminated for a variety of reasons, such as:

- delay or failure in reaching agreement with the FDA or a comparable foreign regulatory authority on a trial design that we are able to execute;

- delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical study;

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delay or failure in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

delay or failure in obtaining institutional review board, or IRB, or IEC approval or the approval of other reviewing entities, including comparable foreign regulatory authorities, to conduct or continue a clinical trial at each site;

withdrawal of clinical trial sites from our clinical trials as a result of changing standards of care or the ineligibility of a site to participate in our clinical trials;

delay or failure in recruiting and enrolling suitable subjects to participate in a trial and/or retaining subjects;

delay or failure in subjects completing a trial or returning for post-treatment follow-up;

clinical sites, subjects, and investigators deviating from trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;

inability to identify and maintain a sufficient number of trial sites, many of which may already be engaged in other clinical trial programs, including some that may be for the same indication;

failure of our third-party clinical trial managers to satisfy their contractual duties or meet expected deadlines;

delay or failure in adding new clinical trial sites;

delay or failure in meeting regulatory agency inspectional requirements;

ambiguous or negative interim results or results that are inconsistent with earlier results;

feedback from the FDA, the IRB or IEC, data safety monitoring boards, or a comparable foreign regulatory authority, or results from earlier stage or concurrent preclinical and clinical studies, that might require modification to the protocol for the trial. For instance, following the interim analysis for our INSPIRE trial, the sample size for the study was increased by 135 subjects. It will thus take us longer and will require a greater investment to complete the study. INSPIRE continues to be conducted under the supervision of the DMC, which may make additional recommendations based upon its continuing safety review;

a study meeting any predefined stopping criteria. For instance, in our Phase I/II expansion study of rigosertib oral in combination with azacitidine, if certain safety results, as defined by the protocol are found, enrollment in the applicable dosing cohort will be stopped;

decision by the FDA, the IRB or IEC, a comparable foreign regulatory authority, or us, or recommendation by a data safety monitoring board or comparable foreign regulatory authority, to suspend or terminate clinical trials at any time for safety issues or for any other reason. For instance, we have previously discontinued enrollment in a Phase 3 study of IV rigosertib following regulatory feedback on the trial's design. We have also discontinued planned trials prior to enrollment due to

changing development plans and the availability of funding.

unacceptable risk-benefit profile, unforeseen safety issues or adverse side effects;

failure to demonstrate a benefit from using a drug;

difficulties in manufacturing, manufacturing quality, or obtaining from third parties sufficient quantities of a product candidate for use in clinical trials;

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lack of adequate funding to continue the clinical trial, including the incurrence of unforeseen costs due to enrollment delays, requirements to conduct additional clinical studies or increased expenses associated with the services of our CROs and other third parties; or

changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial or pay substantial application user fees.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of subjects to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, ability to obtain and maintain patient consents, risk that enrolled subjects will drop out before completion, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages or disadvantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials, and while we have agreements governing their committed activities, we have limited influence over their actual performance.

If we experience delays in the completion or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. In addition, many of the factors that could cause a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may discover, in-license or acquire and seek to develop in the future will ever obtain regulatory approval.

Our product candidates could fail to receive regulatory approval from the FDA or a comparable foreign regulatory authority for many reasons, including:

disagreement over the design or implementation of our clinical trials including as to patient recruitment;

disagreement concerning our choice of patient population and/or other clinical trial design elements, including our chosen endpoint, which may be due to limitations and/or contradictory results in earlier studies;

disagreement with our intended indication;

failure to demonstrate that a product candidate is safe and effective for its proposed indication and/or that our results are clinically relevant;

failure of clinical trials to meet the level of statistical significance required for approval;

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failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;

disagreement over our interpretation of data from preclinical studies or clinical trials;

delay or failure of our manufacturing or clinical trial sites in meeting regulatory agency inspectional requirements;

disagreement over whether to accept efficacy results from clinical trial sites outside the United States or clinical trial sites where the standard of care is potentially different from that in the United States;

disagreement concerning the quality and/or reliability of our study and/or chemistry, manufacturing, and control data

the insufficiency of data collected from clinical trials of our product candidates to support the submission and filing of an NDA or other submission or to obtain regulatory approval;

disapproval of the manufacturing processes or facilities of third-party manufacturers with whom we contract for clinical and commercial supplies; or

changes in the approval policies or regulations that render our preclinical and clinical data insufficient for approval.

The FDA or a comparable foreign regulatory authority may require more information, including additional preclinical or clinical data and or additional chemistry, manufacturing, and control information and/or modifications to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program altogether. For instance, for IV rigosertib for second-line higher-risk MDS patients following failure of HMA therapy, we currently plan to seek NDA approval based on the INSPIRE trial, with supporting data from the ONTIME trial, which did not meet its primary efficacy endpoint. We may also seek approval for other indications and/or product candidates based on a single Phase 3 study. Typically, for FDA approval, FDA requires two adequate and well-controlled Phase 3 clinical trials. For a single Phase 3 study to support approval, the study must be well-designed, well-conducted, internally consistent, and provide statistically persuasive and clinically meaningful results so that a second trial would be ethically or practically impossible to perform. The clinically meaningful results must generally show the effect of the product candidate on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcomes. The FDA or comparable foreign regulatory authorities may find that our studies do not meet this standard, and, in such a case, would require another Phase 3 study to support an NDA or foreign equivalents. Even if we do obtain regulatory approval, our product candidates may be approved for fewer or more limited indications than we request, approval contingent on the performance of costly post-marketing clinical trials, or approval with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. In addition, the FDA may require the establishment of Risk Evaluation Mitigation Strategies, or REMS, or a comparable foreign regulatory authority may require the establishment of a similar strategy, that may restrict distribution of our products and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Approval by the FDA does not ensure approval by foreign regulatory authorities and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other countries 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 others. We may not be able to file for regulatory approvals and even if we file we may not receive the necessary approvals to commercialize our products in any market.

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Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following any marketing approval.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authority. For example, patients in our earlier-stage clinical trials of rigosertib in some cases experienced side effects, some of which were severe. In this 10-K, we have described some of the safety findings for our product candidates. These are not the only safety findings, and we may find other safety outcomes during the course of our clinical trial.

As a result of undesirable side effects or safety or toxicity issues that we may experience in our clinical trials, we may not receive approval to market any product candidates, which could prevent us from ever generating revenues 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 or deny approval of our product candidates for any or all targeted indications. These side effects could affect patient recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. They could also result in restrictive labeling for any approved products.

Additionally, if any of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such product, a number of potentially significant negative consequences could result, including:

- we may be forced to suspend marketing of such product and/or recall such product;
- regulatory authorities may withdraw their approvals of such product;
- regulatory authorities may require additional warnings on the label that could diminish the usage or otherwise limit the commercial success of such products;
- we may be required to conduct post-market studies or establish or modify a REMS or a foreign equivalent;
- we could be sued and held liable for harm caused to subjects or patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved.

Development of a product candidate intended for use in combination with an already approved product may present additional challenges than development of a product candidate for use as a single agent.

We are developing rigosertib both as a single agent and for use in combination with azacitidine, a drug that is already on the market. The development of rigosertib for use in combination with another product may present additional challenges that we will not encounter for the development of our product candidates as single agents. For instance, the design and accompanying data analysis of our clinical trials for rigosertib in combination with azacitidine may be more complex. Following product approval, the FDA may require that rigosertib and/or azacitidine be cross labeled for combination use. As we currently do not own or have rights to azacitidine, this may require us to work with another company to satisfy such a requirement. Moreover, azacitidine developments may impact our clinical trials for the combination as well as our commercial prospects should we receive marketing approval.

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Such developments may include changes to the azacitidine safety or efficacy profile, changes to the availability of azacitidine, and changes to standard of care for MDS.

Even if our product candidates receive regulatory approval, they may still face future development and regulatory difficulties.

Even if we obtain regulatory approval for a product candidate, it would be subject to ongoing requirements by the FDA and comparable foreign regulatory authorities governing the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, marketing, recordkeeping and reporting of safety and other post-market information. The safety profile of any product will continue to be closely monitored by the FDA and comparable foreign regulatory authorities after approval. If the FDA or comparable foreign regulatory authorities become aware of new safety information after approval of any of our product candidates, they may require labeling changes or establishment of a REMS or similar strategy, impose significant restrictions on a product's indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. The label ultimately approved for rigosertib, if it achieves marketing approval, may include restrictions on use. Moreover, any of our product candidates approved under the FDA's accelerated approval pathway will require post-approval studies. If any post-approval studies do not verify the product's clinical benefit or other evidence shows a lack of safety or efficacy, we may be subject to expedited approval withdrawal.

In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities, including comparable foreign regulatory authorities, for compliance with current good manufacturing practices, or cGMP, and other regulations. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market, withdrawal of product approval, requiring us to agree to a REMS or foreign equivalent, requiring us to conduct a Phase IV clinical study, refusal to approve marketing applications or supplements, labeling revisions, adverse publicity, warning letters, untitled letters, dear healthcare provider letters, or suspension of manufacturing. If we, our product candidates, our clinical study sites or contract research organizations, or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements either during product development or following product approval, a regulatory agency may:

- issue warning letters or untitled letters or otherwise unacceptable inspectional findings;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties, disgorgement, restitution, or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical studies or place our studies on clinical hold;
- refuse to approve pending applications or supplements to applications filed by us;

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take FDA debarment actions, take government contracting debarment actions or refuse future orders under existing contracts, take healthcare exclusion actions, or require the entry into corporate integrity agreements or consent decrees;

suspend or impose restrictions on operations, including costly new manufacturing requirements;

seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall; or

subject us or our products to adverse publicity.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate revenue.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by the FDA, the DOJ, the Office of Inspector General of the HHS, state attorneys general, members of Congress and the public. Violations, including promotion of our products for unapproved or off-label uses, are subject to enforcement letters, inquiries and investigations, and civil and criminal sanctions by the FDA. Additionally, advertising and promotion of any product candidate that obtains approval outside of the United States will be heavily scrutinized by comparable foreign regulatory authorities.

In the United States, engaging in impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines and agreements that materially restrict the manner in which we promote or distribute our drug products. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. Since 2004, these False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements based on certain sales practices promoting off-label drug uses. Further, it is expected that the Department of Justice's doubling of civil penalties for violations after November 2015 will encourage more whistleblower lawsuits. This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations, and be excluded from the Medicare, Medicaid and other federal and state healthcare programs. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we are not successful in defending against such actions, those actions could compromise our ability to become profitable.

While rigosertib has received orphan designation for the treatment of MDS in the US and Europe, and while rigosertib has received a similar designation in Japan through our partner SymBio, there is no guarantee that we will be able to maintain this designation, receive this designation for any other product candidate, or receive or maintain any corresponding benefits.

We have received orphan designation for rigosertib for the treatment of MDS in the US and Europe. Our partner SymBio has received similar designation in Japan. We may also seek orphan designation for other indications of rigosertib and other product candidates, as appropriate. Orphan designation in the US or the EU does not guarantee product candidate approval, nor does it guarantee that we will receive any associated benefit, including periods of regulatory exclusivity. Moreover, orphan designation in the US or the EU can be revoked under certain circumstances. In the US, the FDA may revoke an orphan drug designation if the agency finds that the request for designation contained an

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untrue statement of material fact, omitted material information, or if the agency determines that the product candidate was not eligible for the designation at the time of the submission.

Moreover, even if we ultimately receive marketing approval for a product for which we have received orphan designation and associated periods of orphan exclusivity, that exclusivity may not effectively protect the product from competition. Orphan drug exclusivity may be lost for the same reasons orphan designation may be lost 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. Further, orphan exclusivity would only provide limited protections to our product candidates as orphan exclusivity only protects the product from competition from another product with the same principal molecular features for the same indication. Different products can be approved for the same condition or a product with the same molecular features may be able to receive approval for a different indication. Further, even after an orphan product is approved, the FDA can subsequently approve a product containing the same principal molecular features for the same condition if the FDA or EMA concludes that the later product is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care.

Should another company receive approval before us of a product candidate with the same principal molecular features and for the same indication as one of our product candidates, we would be prevented from receiving FDA approval for our product candidate in the United States for at least 7 years (EU 6 years) unless we are able to show that our product candidate is clinically superior. Similarly, if another sponsor receives European approval before we do, we would be prevented from launching our product in the European Union for this indication for a period of at least 10 to 12 years.

Additionally, in response to court cases, the FDA or EU may undertake a reevaluation of aspects of its orphan drug regulations and policies. We do not know if, when, or how the FDA or EU may change the orphan drug regulations and policies, 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, financial condition, results of operations, and prospects could be harmed.

We may not receive anticipated periods of regulatory exclusivity or such exclusivity may not sufficiently protect our product candidates from competition from generic or similar versions of any of our product candidates that receive marketing approval. If this were to occur, the sales of our products could be adversely affected.

Once an NDA is approved, the covered product becomes a "reference listed drug" in the FDA's Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of ANDAs or similar versions of reference listed drugs through the submission of 505(b)(2) applications. Generic products may be significantly less costly to bring to market than the reference listed drug, companies that produce generic products are generally able to offer them at lower prices, and generic products are generally preferred by third-party payors. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug is typically lost to the generic product. FDA and Congress have further recently taken steps to increase generic product competition. Moreover, in addition to generic competition, we could face competition from other companies seeking approval of drug products that are similar to ours using the 505(b)(2) pathway. Such applicants may be able to rely on our product candidates, if approved, or other approved drug products or published literature to develop drug products that are similar to ours. The introduction of a drug product similar to our product candidates could expose us to increased competition. In addition to competition from newly approved products, we may face competition from existing products as medical professionals are not prohibited from using products that are approved for different indications off label.

While there are certain FDA protections for products with remaining patent terms listed in the Orange Book, we must opt to exercise these protections by filing a patent infringement lawsuit within

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45 days of receiving notice of a paragraph IV certification, as described in the Government Regulation section above. If we do not file a patent infringement lawsuit within 45 days of receiving notice of a paragraph IV certification, the ANDA or 505(b)(2) applicant would not be subject to a 30-month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be expensive and time consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products. Accordingly, upon approval of our product candidates we may be subject to generic competition or competition from similar products, or may need to commence patent infringement proceedings, which would divert our resources.

We additionally may not receive any anticipated periods of marketing exclusivity if our product candidates are approved. Even if we receive exclusivity periods, they may not adequately protect our product candidates from competition. For instance, three and five year exclusivity would not prevent other companies from submitting full NDAs. Three year exclusivity would only protect the modifications that are the subject of our marketing applications. Further, a 505(b)(2) applicant could rely on a reference listed drug that is not one of our product candidates, or published literature, in which case any periods of patent or non-patent protection may not prevent FDA making an approval effective. Competition that our products may face from generic or similar versions of our products could materially and adversely impact our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates. Similar issues would arise in the EU and elsewhere.

We may also be eligible in the United States for seven years of orphan exclusivity, which is further discussed above.

Changes in product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates are developed through preclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. During the course of a development program, sponsors may also change the contract manufacturers used to produce the product candidates, as we have done in the case of rigosertib drug substance and, rigosertib intravenous and oral formulations. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of clinical trials. Such changes may also require additional testing, FDA notification, or FDA approval. This could delay completion of clinical trials; require the conduct of bridging clinical trials or studies, or the repetition of one or more clinical trials; increase clinical trial costs; delay approval of our product candidates; and jeopardize our ability to commence product sales and generate revenue.

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

In order to market and sell our products in the European Union and many other jurisdictions, including Japan and Korea, we 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 regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside 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 the

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United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Failure to obtain approval of a product candidate in one jurisdiction could further impact our ability to obtain approval in another jurisdiction. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. If we are unable to obtain approval of any of our product candidates by regulatory authorities in the European Union, Japan, Korea or another country, the commercial prospects of that product candidate may be significantly diminished and our business prospects could decline.

Healthcare legislation, including potentially unfavorable pricing regulations or other healthcare reform initiatives, may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

The regulations that govern, among other things, marketing approvals, coverage, pricing and reimbursement for new drug products vary widely from country to country. In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to successfully sell any product candidates for which we obtain marketing approval. The Patient Protection and Affordable Care Act and the Health Care and Education Affordability Reconciliation Act of 2010, or the Affordable Care Act, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms, any of which could negatively impact our business. The Tax Cuts and Jobs Act of 2017 repealed the individual mandate to purchase health insurance, and other provisions of the Affordable Care Act. In the future other provisions of the Affordable Care Act may be repealed and replaced; however, the downward pressure on pharmaceutical and medical device pricing, especially under the Medicare program is likely to continue, and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several categories of healthcare providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. If we ever obtain regulatory approval and successfully commercialize our product candidates, these new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and accordingly, our financial operations.

In the United States, the European Union and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which has resulted in lower average selling prices. Furthermore, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures

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can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

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 product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product candidate in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country. In the United States, Medicaid and other federal programs impose penalties for increasing prices over the rate of inflation, which can result in penny prices. Some states such as California are also regulating price increases. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates even if our product candidates obtain marketing approval.

Laws and regulations governing international operations may preclude us from developing, manufacturing and selling certain product candidates outside of the United States and require us to develop and implement costly compliance programs.

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

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering 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 the 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 studies 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 as well as personal data relating to identifiable individuals. Our expanding presence outside of the United States will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product 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

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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.

In Europe and elsewhere, most countries have laws (e.g France) or (more commonly) codes of practice which either broadly emulate US 'sunshine laws' and require companies to maintain and publish a record of transfers of value to healthcare professionals and/or have anti-corruption laws similar to the FCPA for instance the UK Bribery Act 2010.

Even if we are able to commercialize our product candidates, the products may not receive coverage and adequate reimbursement from third-party payors, which could harm our business.

Our ability to commercialize any products successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations either in the U.S. or elsewhere. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, determine which medications they will cover and establish reimbursement levels. A primary trend in the U.S. healthcare industry 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 additional clinical evidence, beyond the data required to obtain marketing approval, demonstrating clinical benefits and value in specific patient populations before covering our products for those patients. We cannot be sure that coverage and adequate reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Coverage and reimbursement may impact the demand for, or the price of, any product 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 product candidate for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, established the Medicare Part D program and provided authority for limiting the number of drugs that will be covered in any therapeutic class thereunder. The Medicare Modernization Act, including its cost reduction initiatives, could decrease the coverage and reimbursement rate that we receive for any of our approved products. Furthermore, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that any drug will be paid for in all cases or at a rate that is acceptable to our customers. We may need to provide rebates to third party payors, or co-payment assistance that results in net prices insufficient to 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 only be temporary. 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

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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 obtain coverage and profitable reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenue.

We do not currently have an organization for the sale, marketing and distribution of pharmaceutical products and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market any products that may be approved by the FDA and comparable foreign regulatory authorities, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well-funded sales and marketing operations. Without an internal commercial organization or the support of a third party to perform sales and marketing functions, we may be unable to compete successfully against these more established companies.

Our commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, healthcare payors and the major operators of cancer clinics.

Even if we obtain regulatory approval for any of our product candidates that we may develop or acquire in the future, the product may not gain market acceptance among physicians, healthcare payors, patients or the medical community. Market acceptance of any of our product candidates for which we receive approval depends on a number of factors, including:

- the efficacy and safety of such product candidates as demonstrated in clinical trials;
- the clinical indications for which the product candidate is approved;
- acceptance of such product candidates as a safe and effective treatment by physicians, major operators of cancer clinics and patients;
- the potential and perceived advantages of product candidates over alternative treatments including any potential adverse impact of a product candidate on a patient's quality of life;
- the safety of product candidates seen in broader patient groups, including its use outside the approved indications;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA or other regulatory authorities;
- the timing of market introduction of our products as well as competitive products;
- the cost of treatment in relation to alternative treatments;
- the availability of coverage and adequate reimbursement and pricing by third-party payors and government authorities;

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relative convenience and ease of administration; and

the effectiveness of our sales and marketing efforts and those of our collaborators.

If any of our product candidates are approved but fail to achieve market acceptance among physicians, patients, or healthcare payors, we may not be able to generate significant revenues, which would compromise our ability to become profitable.

Our relationships with customers 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 all play important roles in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers 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 would market, sell and distribute our products. As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. Additionally, if we sell to government agencies, these sales will be constrained by laws imposing mandatory discounts and federal procurement regulations. Restrictions under applicable federal and state healthcare laws and regulations and comparable foreign laws that may affect our ability to operate include the following:

the federal healthcare Anti-Kickback Statute will constrain our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, 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 of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

federal civil and criminal false claims laws and civil monetary penalty laws impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement that causes us to avoid, decrease or conceal an obligation to pay money to the federal government;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal liability for executing a scheme to defraud any healthcare benefit program and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services;

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

the federal physician sunshine requirements under the Affordable Care Act requires manufacturers of drugs, devices, biologics and medical supplies to report annually to HHS information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and

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other healthcare providers and their immediate family members and applicable group purchasing organizations;

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report pricing information and information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and

state and foreign laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. For instance the forthcoming (25 May 2018) EU General Data Protection Regulation imposes stricter rules on the processing of personal data than apply in the USA and its provisions exclude the export of data relating to identifiable individuals to most countries, including the US, unless certain safeguards are in place.

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 from government funded healthcare programs, such as Medicare and Medicaid, debarment from government contracts, and the curtailment or restructuring of our operations. If any physicians or other healthcare providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Our employees may engage in misconduct or other improper activities, including noncompliance 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, Centers for Medicare & Medicaid Services, 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, comply with FDA's laws and regulations, 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. We have adopted a code of conduct for our directors, officers and employees, but 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 or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, rigosertib, briciclib and recilisib, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Our product candidates are being developed for cancer therapeutics and radiation protection. There are a variety of available therapies and supportive care products marketed for cancer patients. In many cases, these drugs are administered in combination to enhance efficacy or to reduce side effects. 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 or products and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. This may make it difficult for us to achieve market acceptance at desired levels in a timely manner to ensure viability of our business.

More established companies may have a competitive advantage over us due to their greater size, cash flows and institutional experience. Compared to us, many of our competitors may have significantly greater financial, technical and human resources.

As a result of these factors, our competitors may obtain regulatory approval of their products before we are able to obtain patent protection or other intellectual property rights which will limit our ability to develop or commercialize our product candidates. Our competitors may also develop drugs that are safer, more effective, more widely used and cheaper than ours, and may also be more successful than us in manufacturing and marketing their products. These appreciable advantages could render our product candidates obsolete or non-competitive before we can recover the expenses of development and commercialization.

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, management and commercial personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If we breach our license agreements or fail to negotiate new agreements pertaining to our product candidates, we could lose the ability to continue the development and potential commercialization of these product candidates.

In January 1999, we entered into an agreement with Temple University, as subsequently amended, to obtain an exclusive, world-wide license to make, have made, use, sell, offer for sale and import several classes of novel compounds, including all three of our clinical-stage product candidates. In May 2010, we entered into an agreement with Mount Sinai School of Medicine, as subsequently amended, giving us the option to exclusively negotiate licenses related to certain compounds. If we fail to meet

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our obligations under these license agreements or if we fail to negotiate future license agreements, our rights under the licenses could be terminated, and upon the effective date of such termination, our right to use the licensed technology would terminate. While we would expect to exercise all rights and remedies available to us, including attempting to cure any breach by us, and otherwise seek to preserve our rights under the patents and other technology licensed to us, we may not be able to do so in a timely manner, at an acceptable cost or at all. Any uncured, material breach under the license agreement could result in our loss of exclusive rights and may lead to a complete termination of our product development and any commercialization efforts for the applicable product candidates.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. Product liability claims may be brought against us by subjects enrolled in our clinical trials, and patients, healthcare providers or others using, administering or selling our products in third party studies, expanded access programs, or commercially, if we receive product approval. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for any product candidates or products that we may develop;

termination of clinical trial sites or entire trial programs;

actions by regulatory authorities, including clinical holds and withdrawal of product approvals;

injury to our reputation and significant negative media attention;

withdrawal of clinical trial participants;

significant costs to defend the related litigation;

substantial monetary awards to trial subjects or patients;

loss of revenue;

diversion of management and scientific resources from our business operations; and

the inability to commercialize any products that we may develop.

We currently hold $10.0 million in product liability insurance coverage in the aggregate, which may not be adequate to cover all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. We intend to expand our insurance coverage for products to include the sale of commercial products if we obtain marketing approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us, particularly if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

Our future success depends on our ability to retain our executive officers and to attract, retain and motivate qualified personnel.

We are highly dependent upon Ramesh Kumar, Ph.D., President and Chief Executive Officer; Manoj Maniar, Ph.D., Senior Vice President, Product Development; Steven Fruchtman, M. D., Chief

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Medical Officer and Senior Vice President, Research and Development; Mark Guerin, C.P.A., Chief Financial Officer; and our other executive officers. Although we have employment agreements with the persons named above, these agreements are at-will and do not prevent such persons from terminating their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees, other than our President and Chief Executive Officer. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

If we are unable to attract and retain highly qualified employees, we may not be able to grow effectively.

Our future and success depend on our ability to retain, manage and motivate our employees. During 2015 and 2016, we reduced our headcount in order to conserve cash. These activities, along with any other actions we are taking or may take to conserve cash, may make it more difficult to retain key employees. The loss of any member of our senior management team or the inability to hire or retain experienced management personnel could compromise our ability to execute our business plan and harm our operating results. Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. The competition for qualified personnel in the pharmaceutical field is intense and as a result, we may be unable to continue to retain qualified personnel necessary for the development of our business. In addition, if our development plans are successful, we will need additional managerial, operational, sales, marketing, financial and other resources, and may find it more difficult to attract such qualified personnel.

We may engage in future business combinations that could disrupt our business, cause dilution to our stockholders and harm our financial condition and operating results.

While we currently have no specific plans to acquire any other businesses, we may, in the future, make acquisitions of, or investments in, or otherwise engage in business combinations with companies that we believe have products or capabilities that are a strategic or commercial fit with our current product candidates and business or otherwise offer opportunities for our company. In connection with these acquisitions or investments, we may:

issue stock that would dilute our existing stockholders' percentage of ownership;

incur debt and assume liabilities; and

incur amortization expenses related to intangible assets or incur large and immediate write-offs.

We may not be able to complete any future business combination on favorable terms, if at all. If we do complete a business combination, we cannot assure you that it will ultimately strengthen our competitive position or that it will be viewed positively by customers, financial markets or investors. Furthermore, future business combinations could pose numerous additional risks to our operations, including:

problems integrating the businesses, products or technologies;

increases to our expenses;

the failure to discover undisclosed liabilities of an acquired asset or transaction partner;

diversion of management's attention from their day-to-day responsibilities;

harm to our operating results or financial condition;

entrance into markets in which we have limited or no prior experience; and

potential loss of key employees.

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We may not be able to complete any business combination or effectively integrate the operations, products or personnel gained through any such business combination.

Our business and operations would suffer in the event of computer system failures.

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, fire, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical trial data from 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 results in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

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 the success of 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 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 or hazardous 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 production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Business disruptions could seriously harm our future revenues and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce our product candidates. Our ability to obtain clinical supplies of product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. The ultimate impact on us, our significant suppliers and our general infrastructure of being consolidated in certain geographical areas is unknown, but our operations and financial condition could suffer in the event of a major earthquake, fire or other natural disaster.

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We are relying on the FDA's "Animal Efficacy Rule" to demonstrate efficacy of recilisib, which could result in delays or failure at any stage of recilisib's development process, increase our development costs and adversely affect the commercial prospects of recilisib.

Because humans are not normally exposed to radiation and it would be unethical to expose humans to such, effectiveness of recilisib cannot be demonstrated in humans, but instead, under the FDA's "Animal Efficacy Rule," can be demonstrated, in part, by utilizing animal models. This effect has to be demonstrated in more than one animal species expected to be predictive of a response in humans, but an effect in a single animal species may be acceptable if that animal model is sufficiently well-characterized for predicting a response in humans. The animal study endpoint must be clearly related to the desired benefit in humans and the information obtained from animal studies must allow selection of an effective dose in humans. Safety may be demonstrated in human studies.

We may not be able to sufficiently demonstrate the animal correlation to the satisfaction of the FDA, as these correlates are difficult to establish and are often unclear. The FDA may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies, refuse to approve recilisib, or place restrictions on our ability to commercialize recilisib. Furthermore, other countries, at this time, have not established criteria for review and approval of these types of products outside their normal review process. There is no "Animal Efficacy Rule" equivalent in countries other than the United States, and consequently there can be no assurance that we will be able to make a submission for marketing approval in foreign countries based on such animal data.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our preclinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We have relied upon and plan to continue to rely upon third-party CROs to monitor and manage data for our ongoing preclinical and clinical programs, as well as clinical trial sites for the conduct of our clinical trials. We rely on these parties for execution of our preclinical and clinical trials, and we control only some aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the CROs and sites does not relieve us of our regulatory responsibilities. We also rely on third parties to assist in conducting our preclinical studies in accordance with Good Laboratory Practices, or GLP, and the Animal Welfare Act requirements. We, our clinical trial sites, and our CROs are required to comply with federal regulations and current Good Clinical Practices, or GCP, which are international standards meant to protect the rights and health of patients that are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce GCP through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our sites or CROs fail to comply with applicable GCP, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We or they may also face regulatory enforcement. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. In addition, our clinical trials must be conducted with product produced under cGMP requirements. Failure to comply with these regulations may require us to repeat preclinical and clinical trials, which would delay the regulatory approval process. We may also face liability and/or regulatory enforcement action should any of the third parties that we rely upon fail to comply with legal and/or regulatory requirements.

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Our CROs and the employees at clinical sites are not our employees, and except for remedies available to us under our agreements with such CROs and sites, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, nonclinical and preclinical programs. If CROs or sites do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Because we have relied on third parties, our internal capacity to perform these functions is limited. Outsourcing these functions involves risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. Though we carefully manage our relationships with our CROs and clinical trial sites, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

If we lose our relationships with CROs, our drug development efforts could be delayed.

We rely on third-party vendors and CROs for preclinical studies and clinical trials related to our drug development efforts. Switching or adding additional CROs would involve additional cost and requires management time and focus. Our CROs have the right to terminate their agreements with us in the event of an uncured material breach. In addition, some of our CROs have an ability to terminate their respective agreements with us if it can be reasonably demonstrated that the safety of the subjects participating in our clinical trials warrants such termination, if we make a general assignment for the benefit of our creditors or if we are liquidated. We may also terminate a CRO for a number of reasons. Identifying, qualifying and managing performance of third-party service providers can be difficult, time consuming and cause delays in our development programs. In addition, there is a natural transition period when a new CRO commences work and the new CRO may not provide the same type or level of services as the original provider. If any of our relationships with our third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms.

We have limited experience manufacturing our product candidates on a large clinical or commercial scale and have no manufacturing facility. We are dependent on third-party manufacturers for the manufacture of our product candidates for clinical trials as well as on third parties for our supply chain, and if we experience problems with any third parties, the manufacturing of our product candidates or products could be delayed.

We do not own or operate facilities for the manufacture of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. We currently rely on a single source contract manufacturing organization, or CMO, for the chemical manufacture of active pharmaceutical ingredient for rigosertib, another CMO for the production of the rigosertib intravenous formulation for our Phase 3 clinical trial, and a third CMO for the production of the rigosertib oral formulation for a Phase 2 clinical trial. To meet our projected needs for clinical supplies to support our activities through regulatory approval and commercial manufacturing, the CMOs with whom we currently work will need to increase the scale of production. We may need to identify

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additional CMOs for continued production of supply for our product candidates. In addition, regulatory authorities enforce cGMP through periodic inspections of active pharmaceutical ingredient, or API and drug product manufacturing sites, quality control contract laboratories and distribution centers. If we or our CMO fail to comply with applicable cGMP, the manufacturing data generated and subsequent API lots and drug product batches in our supply chain may be deemed unreliable. Clinical trials using the product candidate may also be deemed to be unreliable. As such, the FDA or comparable foreign regulatory authorities may require us to perform additional API and drug product manufacturing before continuing clinical trials or approving our marketing applications, may require us to conduct additional studies, and any such deficient product we supply to SymBio or any other collaboration partner may subject us to certain obligations under relevant agreements. We or our contractors may also face enforcement actions. For example, in 2013, we began preparing a second CMO for potential manufacture of API and incurred significant expense to do so. Additionally, for example, during the second quarter of 2016, we suspended the original CMO for manufacture of the rigosertib oral formulation for quality related reasons, and transferred manufacturing activities to a new CMO leaving us again with a single source of manufacture for this formulation for our continuing development of rigosertib oral in combination with azacitidine. We have not yet identified alternate suppliers in the event the current CMOs we utilize are unable to scale production, or if we otherwise experience any problems with them. Although alternative third-party suppliers with the necessary manufacturing and regulatory expertise and facilities exist, as we have experienced with respect to our existing CMOs, it could be expensive and take a significant amount of time to arrange for alternative suppliers. If we are unable to arrange for alternative third-party manufacturing sources, or to do so on commercially reasonable terms or in a timely manner, we may not be able to complete development of our product candidates, or market or distribute them.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates or products ourselves, including reliance on the third party for regulatory compliance and quality assurance, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control, including a failure to synthesize and manufacture our product candidates or any products we may eventually commercialize in accordance with our specifications, and the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or damaging to us. In addition, the FDA and other regulatory authorities require that our product candidates and any products that we may eventually commercialize be manufactured according to cGMP and similar foreign standards. Any failure by our third-party manufacturers to comply with cGMP or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates. In addition, such failure could be the basis for the FDA to issue a warning letter, withdraw approvals for product candidates previously granted to us, or take other regulatory or legal action, including recall or seizure of outside supplies of the product candidate, total or partial suspension of production, suspension of ongoing clinical trials, refusal to approve pending applications or supplemental applications, detention or product, refusal to permit the import or export of products, injunction, or imposing civil and criminal penalties. The manufacturing facilities that we use must also be approved by FDA under a pre-approval inspection. If the facilities cannot pass these inspections, FDA will not approve our marketing application. These manufacturing facilities will further be subject to continuing regulatory oversight and inspection, and, thus, they must continue to expend time and resources to maintain regulatory compliance.

Any significant disruption in our supplier relationships could harm our business. Any significant delay in the supply of a product candidate or its key materials for an ongoing clinical study could considerably delay completion of our clinical studies, product testing and potential regulatory approval of our product candidates. If our manufacturers or we are unable to purchase these key materials after regulatory approval has been obtained for our product candidates, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates.

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We have entered into collaboration agreements with SymBio and Baxalta for rigosertib development and commercialization in certain territories and we may elect to enter into additional licensing or collaboration agreements to partner rigosertib in territories currently retained by us. Our dependence on such relationships may adversely affect our business.

Because we have limited resources, we seek to enter into, and in the past we have entered into, collaboration agreements with other pharmaceutical companies. We may elect to enter into more of these agreements in the future. In July 2011, we entered into a license agreement with SymBio, as subsequently amended, granting an exclusive, royalty-bearing license for the development and commercialization of rigosertib in Japan and Korea, and related ancillary supply agreement and quality agreement. In September 2012, we entered into a development and license agreement with Baxter Healthcare SA, which subsequently assigned its interest in the agreement to Baxalta. Our agreement with Baxalta, which was terminated August 30, 2016, had granted it an exclusive, royalty-bearing license for the development and commercialization of rigosertib in specified countries comprising most of Europe. In March 2018, we entered into a license agreement with Pint granting an exclusive, royalty-bearing license for the development and commercialization of rigosertib in South and Central America. Any failure by our current or future partners to perform their obligations or any decision by our partners to terminate our agreements, including the termination of the Baxalta agreement, or our failure to meet our obligations under such agreements, could reduce or terminate the funding we may receive under the relevant collaboration agreement and could subject us to financial obligations and negatively impact our ability to successfully develop, obtain regulatory approvals for and commercialize the applicable product candidate. In the event that any of our partners fails to comply with applicable regulatory requirements, FDA or foreign regulatory authorities may not accept the data that they generate in furtherance of our marketing applications, and they or us could be subject to enforcement action. In addition, any decision by our partners to terminate these agreements could also damage our reputation and negatively impact our ability to obtain financing from other sources.

We may not achieve the milestones set forth in our collaboration agreements, or may disagree with our collaboration partners as to whether certain milestones have been met. Any such failure or disagreement would negatively impact our potential funding sources if we are unable to receive the contemplated milestone payments.

Our commercialization strategy for rigosertib in territories currently retained by us may depend on our ability to enter into agreements with collaborators to obtain assistance and funding for the development and potential commercialization of rigosertib in those territories. Despite our efforts, we may be unable to secure additional collaborative licensing or other arrangements that are necessary for us to further develop and commercialize rigosertib. Supporting diligence activities conducted by potential collaborators and negotiating the financial and other terms of a collaboration agreement are long and complex processes with uncertain results. Even if we are successful in entering into one or more collaboration agreements, collaborations may involve greater uncertainty for us, as we have less control over certain aspects of our collaborative programs than we do over our proprietary development and commercialization programs. We may determine that continuing a collaboration under the terms provided is not in our best interest, and we may terminate the collaboration. Our collaborators could delay or terminate their agreements, and as a result rigosertib may never be successfully commercialized.

Further, collaborators may develop alternative products or pursue alternative technologies either on their own or in collaboration with others, including our competitors, and the priorities or focus of our collaborators may shift such that rigosertib receives less attention or resources than we would like, or they may be terminated altogether. Any such actions by our collaborators may adversely affect our business prospects and ability to earn revenues. In addition, we could have disputes with our current or future collaborators, such as the interpretation of terms in our agreements. Any such disagreements

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could lead to delays in the development or commercialization of rigosertib or could result in time-consuming and expensive litigation or arbitration, which may not be resolved in our favor.

With respect to our programs that are currently not the subject of collaborations, we may enter into agreements with collaborators to share in the burden of conducting clinical trials, manufacturing and marketing these product candidates. In addition, our ability to develop additional proprietary compounds may depend on our ability to establish and maintain licensing arrangements or other collaborative arrangements with the holders of proprietary rights to such compounds. We may not be able to establish such arrangements on favorable terms or at all, and our future collaborative arrangements may not be successful.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property rights, our competitive position could be harmed.

We depend on our ability to protect our proprietary technology. We rely on trade secret, patent, copyright and trademark laws, and confidentiality, licensing and other agreements with employees and third parties, all of which offer only limited protection. Our commercial success will depend in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. Where we have the right to do so under our license agreements, we seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and products that are important to our business. The patent positions of biotechnology and pharmaceutical companies generally are highly uncertain, involve complex legal and factual questions and have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patents, including those patent rights licensed to us by third parties, are highly uncertain.

The steps we have taken to protect our proprietary rights may not be adequate to preclude misappropriation of our proprietary information or infringement of our intellectual property rights, both inside and outside the United States. The rights already granted under any of our currently issued patents and those that may be granted under future issued patents may not provide us with the proprietary protection or competitive advantages we are seeking. If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection obtained is not sufficient, our competitors could develop and commercialize technology and products similar or superior to ours, and our ability to successfully commercialize our technology and products may be adversely affected.

With respect to patent rights, we do not know whether any of the pending patent applications for any of our licensed compounds will result in the issuance of patents that protect our technology or products, or if any of our issued patents will effectively prevent others from commercializing competitive technologies and products. Our pending applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Further, the examination process may require us or our licensor to narrow the claims for our pending patent applications, which may limit the scope of patent protection that may be obtained if these applications issue. Because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, issued patents that we own or have licensed from third parties may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in the loss of patent protection, the narrowing of claims in such patents or the invalidity or unenforceability of such patents, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection for our technology and products. Protecting against the unauthorized use of our patented technology, trademarks and other intellectual property rights is expensive, difficult and may in some cases not be possible. In some cases, it may be difficult or impossible to detect third-party infringement

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or misappropriation of our intellectual property rights, even in relation to issued patent claims, and proving any such infringement may be even more difficult.

We could be required to incur significant expenses to perfect our intellectual property rights, and our intellectual property rights may be inadequate to protect our competitive position.

The patent prosecution process is expensive and time-consuming, and we or our licensors 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 or our licensors will fail to identify patentable aspects of inventions made in the course of our development and commercialization activities before it is too late to obtain patent protection on them. Further, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the expiration of the patent. However, the applicable authorities, including the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. 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, and these foreign laws may also be subject to change. For example, methods of treatment and manufacturing processes may not be patentable in certain jurisdictions. 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 or our licensors were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a "first to file" system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the U.S. Patent and Trademark Office, or the USPTO, and may become involved in opposition, derivation, reexamination, inter partes review, post grant 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, which could adversely affect our competitive position.

Many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, did not become effective until March 16, 2013. Currently, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

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Obtaining and maintaining our patent protection depends on compliance with various procedural, document submissions, 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 on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance 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. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, our competitive position would be adversely affected.

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

Competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, litigation may be necessary in the future to enforce or defend our intellectual property rights, to protect our trade secrets or to determine the validity and scope of our own intellectual property rights or the proprietary rights of others. This can be expensive and time consuming. Many of our current and potential competitors have the ability to dedicate substantially greater resources to defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating our intellectual property. Litigation could result in substantial costs and diversion of management resources. In addition, in an infringement proceeding, a court may decide that a patent owned by or licensed to us is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could harm our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates, and to 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 products and technology, including interference or derivation proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and commercializing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, in any such proceeding or litigation, we could be found liable for monetary damages. A finding of infringement

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could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets 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, including our senior management, were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. 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. We are not aware of any threatened or pending claims related to these matters or concerning the agreements with our senior management, but in the future litigation may be necessary to defend against 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.

We may be subject to claims by third parties claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other technology or pharmaceutical companies, including our competitors or potential competitors. It is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us.

However, a Licensor of intellectual property to us may not be successful in executing such agreements concerning its intellectual property and/or we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Their and our assignment agreements may not be self-executing or may be breached or found otherwise defective, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our licensed or owned intellectual property. If we fail in prosecuting or 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 prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property disputes 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 substantial adverse effect on the market 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

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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 compromise our ability to compete in the marketplace.

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 some of our technology and products, 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, corporate collaborators, outside scientific collaborators, CMOs, consultants, advisors and other third parties. We also generally enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. 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 both within and outside the United States may be 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 such competitor from using that technology or information to compete with us, which could harm our competitive position.

Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret, In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products, and may export otherwise infringing products to territories where we have patent protection, but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

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Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make compounds that are the same as or similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or our licensors or any strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or our licensors or any strategic partners might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- It is possible that our pending patent applications will not lead to issued patents.
- Issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.
- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.

Risks Related to Ownership of Our Common Stock

We are not in compliance with the Nasdaq continued listing requirements. If we are unable to comply with the continued listing requirements of the Nasdaq Capital Market, Common Stock could be delisted, which could affect Common Sock's market price and liquidity and reduce our ability to raise capital.

We are required to meet certain qualitative and financial tests to maintain the listing of our securities on The Nasdaq Capital Market. As previously disclosed, as of March 31, 2017, June 30, 2017 and September 30, 2017, our total stockholders' equity was $(2.7) million, $0.4 million and $(6.1) million, respectively. As of December 31, 2017 our total stockholders' equity was $(10.9) million. As a result, we did not comply with the Nasdaq's $2.5 million minimum stockholders' equity requirement, nor the alternative compliance standards under Nasdaq Listing Rule 5550(b) for the continued listing of our securities on The Nasdaq Capital Market. In addition, as previously disclosed, the Nasdaq Staff notified us of the noncompliance and, after granting certain grace period and reviewing our proposed plan to regain compliance, the Nasdaq Staff had determined to seek to delist our securities from Nasdaq unless we requested a hearing before a Nasdaq Hearings Panel (the "Panel"). Accordingly, we requested and had a hearing on January 18, 2018 before the Panel, which has the authority to grant us an additional extension of time to regain compliance.

On February 2, 2018, we received a letter from the Panel stating that the Panel has granted the Company an extension to April 13, 2018 to regain compliance with the continuing listing requirements

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of the Nasdaq Capital Market, which may be accomplished by demonstrating minimum stockholders' equity of $2.5 million or having the market value of listed securities of at least $35 million for ten consecutive trading days, as defined in Nasdaq Listing Rule 5550(b).

There is no assurance that we will regain compliance on or before April 13, 2018, and even if we do, that we will be able to maintain compliance. If we are unable to regain compliance by April 13, 2018 or maintain compliance and our securities are delisted, it could be more difficult to buy or sell our securities and to obtain accurate quotations, and the price of our securities could suffer a material decline. Delisting could also impair our ability to raise capital.

The trading market in our common stock has been limited and substantially less liquid than the average trading market for a stock quoted on the Nasdaq Markets.

Since our initial listing on the Nasdaq Global Select Market on July 25, 2013 and transfer to the Nasdaq Capital Market on February 5, 2016, the trading market in our common stock has been limited and substantially less liquid than the average trading market for companies listed on the Nasdaq exchange. The listing of our common stock on the Nasdaq Capital Market does not assure that a meaningful, consistent and liquid trading market currently exists. We cannot predict whether a more active market for our common stock will develop in the future. An absence of an active trading market could adversely affect our stockholders' ability to sell our common stock at current market prices in short time periods, or possibly at all. Additionally, market visibility for our common stock may be limited and such lack of visibility may have a depressive effect on the market price for our common stock. As of February 28, 2018, approximately 48% of our outstanding shares of common stock was held by our officers, directors, beneficial owners of 5% or more of our capital stock and their respective affiliates, which adversely affects the liquidity of the trading market for our common stock, in as much as federal securities laws restrict sales of our shares by these stockholders. If our affiliates continue to hold their shares of common stock, there will be limited trading volume in our common stock, which may make it more difficult for investors to sell their shares or increase the volatility of our stock price.

Our share price may be volatile and result in substantial losses to our stockholders.

The trading price of our common stock is highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Between January 1, 2016 and December 31, 2017, the price of our common stock on the Nasdaq Stock Market has ranged from $10.30 per share to $1.21 per share. Factors that could impact the trading price of our common stock include, without limitation, the following:

- results of clinical trials of our product candidates or those of our competitors;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated changes in our growth rate relative to our competitors;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the success of competitive products or technologies;
- 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 product candidates or clinical development programs;

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the results of our efforts to in-license or acquire additional product candidates or products;

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;

fluctuations in the valuation of companies perceived by investors to be comparable to us;

share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;

announcement or expectation of additional financing efforts;

sales of our common stock by us, our insiders or our other stockholders;

changes in the structure of healthcare payment systems;

market conditions in the pharmaceutical and biotechnology sectors; and

general economic, industry and market conditions.

In addition, the stock market in general, and pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. The realization of any of these risks or any of a broad range of other risks could have a dramatic and material adverse impact on the market price of our common stock.

We may be subject to securities litigation, which is expensive and could divert management attention.

In the past companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. Likewise, companies that have experienced a clinical hold, as we have with one of our secondary compounds, have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors and holders of five percent or more of our capital stock, in the aggregate beneficially owned approximately 48% of our voting stock at February 28, 2018. These stockholders may be able to determine the outcome of all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

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We are an "emerging growth company" and a "smaller reporting company" and we take advantage of reduced disclosure and governance requirements applicable to emerging growth companies, which could result in our common stock being less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and we take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We may take advantage of these reporting exemptions until we are no longer an emerging growth company, which in certain circumstances could be until December 31, 2018. In addition, we are also a "smaller reporting company" as defined in Rule 12b-2 of the Exchange Act and are eligible for certain reduced disclosure requirements.

We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, it may be difficult for us to raise additional capital as and when we need it. Investors may be unable to compare our business with other companies in our industry if they believe that our financial accounting is not as transparent as other companies in our industry. If we are unable to raise additional capital as and when we need it, our financial condition and results of operations may be materially and adversely affected.

If we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. Under Section 404 of the Sarbanes-Oxley Act, we are required to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting. This assessment includes disclosure of any material weaknesses identified by our management in our internal control over financial reporting. Section 404 of the Sarbanes-Oxley Act also generally requires an attestation from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting. However, for as long as we remain an "emerging growth company" or a "smaller reporting company", we intend to utilize the provision exempting us from the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. In addition, any such failure could result in a loss of investor confidence in the accuracy and completeness of our financial reports and a decline in our stock price, and we could be subject to sanctions or investigations by the Nasdaq Stock Market, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

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Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations. To raise capital, we may sell substantial amounts of common stock or securities convertible into or exchangeable for common stock. These future issuances of common stock or common stock-related securities, together with the exercise of outstanding options and any additional shares issued in connection with acquisitions, if any, may result in material dilution to our investors. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common stock.

See " Risks Related to Our Financial Position and Capital Needs Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates" for a discussion of risks related to future issuances of securities for capital raising and strategic transactions.

In addition, future option grants and issuances of common stock, under our 2013 Equity Compensation Plan, and warrants may have an adverse effect on the market price of our common stock. Pursuant to our equity incentive plans, our compensation committee is authorized to grant equity-based incentive awards to our directors, executive officers and other employees and service providers, including officers, employees and service providers of our subsidiaries and affiliates. At December 31, 2017, there were 894,996 shares of our common stock underlying outstanding options and 57,632 shares available for future grant under our 2013 Equity Compensation Plan. In accordance with the terms of the 2013 Equity Compensation Plan, on January 1, 2018, the maximum aggregate number of shares of our common stock that may be issued under the plan was automatically increased by 200,000 shares, such that immediately after such increase the number of shares remaining available for future issuance under the plan was 257,632. At February 28, 2018, we had 5,067,271 warrants outstanding. Future option grants and issuances of common stock under our 2013 Equity Compensation and warrants may have an adverse effect on the market price of our common stock.

The sale or issuance of our common stock to Lincoln Park Capital Fund LLC, or Lincoln Park, may cause dilution and the sale of the shares of common stock acquired by Lincoln Park, or the perception that such sales may occur, could cause the price of our common stock to fall.

In October 2015, we entered into a purchase agreement with Lincoln Park, pursuant to which Lincoln Park has committed to purchase up to $16,500,000 of our common stock. Concurrently with the execution of the purchase agreement, Lincoln Park purchased 84,675 shares of our common stock for

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total proceeds of $1,500,000 and we issued 20,000 shares of our common stock to Lincoln Park as a fee for its commitment to purchase shares of our common stock under the purchase agreement. We may sell shares to Lincoln Park at our discretion from time to time over a 36-month period which commenced November 3, 2015, after the SEC declared effective a registration statement covering the resale of shares we have sold and may sell in the future to Lincoln Park under the purchase agreement. The purchase price for the shares that we may sell to Lincoln Park under the purchase agreement will fluctuate based on the market price of our common stock. Depending on market liquidity at the time, sales of such shares may cause the trading price of our common stock to fall.

We generally have the right to control the timing and amount of any sales of our shares to Lincoln Park. Additional sales of our common stock, if any, to Lincoln Park will depend upon market conditions and other factors to be determined by us. Lincoln Park may ultimately purchase all, some or none of the shares of our common stock that may be sold pursuant to the purchase agreement and, after it has acquired shares, Lincoln Park may sell all, some or none of those shares. Therefore, sales to Lincoln Park by us could result in substantial dilution to the interests of other holders of our common stock. Additionally, the sale of a substantial number of shares of our common stock to Lincoln Park, or the anticipation of such sales, could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sales.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our tenth amended and restated certificate of incorporation, or Certificate of Incorporation, and amended and restated bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders, or remove our current management. These include provisions that will:

- permit our board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate (as of February 28, 2018, we had no shares of preferred stock issued and outstanding, and 1,044,488 shares of Series A Convertible Preferred Stock reserved for issuance upon the exercise of outstanding preferred stock warrants);

- provide that all vacancies on our board of directors, including as a result of newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;

- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;

- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;

- not provide for cumulative voting rights, thereby allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election; and

- provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons requested by a majority of the board of directors to call such meetings.

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

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of directors, who are responsible for appointing the members of our management. Because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may discourage, delay or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our stockholders. Under Delaware law, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other things, the board of directors has approved the transaction. Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

ITEM 1B. ***UNRESOLVED STAFF COMMENTS***

None.

ITEM 2. ***PROPERTIES***

Our corporate headquarters and research facilities are located in Newtown, Pennsylvania, where we lease an aggregate of approximately 9,500 square feet of office and laboratory space, pursuant to lease agreements, the terms of which expire in February 2019.

We believe that our Newtown, Pennsylvania facility is adequate for our near-term needs. When our lease expires, we may exercise renewal options or look for additional or alternate space for our operations. We believe that suitable additional or alternative space would be available on commercially reasonable terms if required in the future.

ITEM 3. ***LEGAL PROCEEDINGS***

We are not a party to any legal proceedings and we are not aware of any such proceedings contemplated by government authorities.

ITEM 4. ***MINE SAFETY DISCLOSURES***

Not applicable.

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PART II

ITEM 5. *MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES*

Market Information

Our common stock began trading on the Nasdaq Global Select Market on July 25, 2013 under the symbol "ONTX." In February 2016, we transferred the listing of our common stock to the Nasdaq Capital Market. The following table sets forth the high and low sales prices per share of our common stock as reported on the Nasdaq Global Select Market or Nasdaq Capital Market for the period indicated.

	High	Low
Year Ended December 31, 2017		
First Quarter	$ 3.34	$ 2.20
Second Quarter	3.88	1.78
Third Quarter	2.21	1.46
Fourth Quarter	2.83	1.21
Year Ended December 31, 2016		
First Quarter	$ 10.30	$ 3.20
Second Quarter	8.17	3.80
Third Quarter	5.93	2.62
Fourth Quarter	3.67	2.11

The share prices have been retroactively adjusted to reflect a one-for-ten reverse stock split which was effective May 31, 2016.

Stockholders

As of February 28, 2018, there were 141 holders of record for shares of our common stock. This does not reflect beneficial stockholders who held their common stock in "street" or nominee name through brokerage firms.

Securities Authorized for Issuance Under Equity Compensation Plans

Information regarding securities authorized for issuance under the Company's equity compensation plans is contained in Part III, Item 11 of this Annual Report.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future.

ITEM 6. *SELECTED FINANCIAL DATA*

As a smaller reporting company, the Company is not required to provide the information otherwise required by this Item.

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ITEM 7. ***MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS***

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes and other financial information included elsewhere in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should review the "Risk Factors" section of this Annual 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.

Overview

We are a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule product candidates primarily to treat cancer. Using our proprietary chemistry platform, we have created an extensive library of targeted agents designed to work against cellular pathways important to cancer cells. We believe that the product candidates in our pipeline have the potential to be efficacious in a variety of cancers. We have one Phase 3 clinical-stage product candidate and two other clinical-stage product candidates (one of which is being developed for treatment of acute radiation syndromes) and several preclinical programs. Substantially all of our current effort is focused on our lead product candidate, rigosertib. Rigosertib is being tested in an intravenous formulation as a single agent, and an oral formulation in combination with azacitidine, in clinical trials for patients with higher-risk myelodysplastic syndromes ("MDS").

We were incorporated in Delaware in December 1998 and commenced operations in January 1999. Our operations to date have included our organization and staffing, business planning, raising capital, in-licensing technology from research institutions, identifying potential product candidates, developing product candidates and building strategic alliances, as well as undertaking preclinical studies and clinical trials of our product candidates.

Since commencing operations, we have dedicated a significant portion of our resources to the development of our clinical-stage product candidates, particularly rigosertib. We incurred research and development expenses of $19.1 million and $20.1 million during the years ended December 31, 2017 and 2016, respectively. We anticipate that a significant portion of our operating expenses will continue to be related to research and development as we continue to advance our programs. In July 2013, we completed our initial public offering, or IPO, from which we received net proceeds of $79.8 million. Prior to the consummation of the IPO, we funded our operations primarily through the sale of preferred stock amounting to $144.7 million, the issuance of debt amounting to $26.8 million, which was later converted into shares of preferred stock, the receipt of $8.0 million from The Leukemia and Lymphoma Society under a May 2010 funding agreement, and the receipt of upfront payments of $57.5 million from Baxter (predecessor to Baxalta) and SymBio in connection with our collaboration agreements. Under the Baxalta collaboration agreement, we received payments towards costs for the INSPIRE trial of $0.0 million and $5.0 million during the years ended December 31, 2017 and 2016, respectively. The Baxalta agreement was terminated on August 30, 2016 as a result of Baxalta's decision to terminate following its strategic review of priorities.

In December 2017, we entered into a license and collaboration agreement with HanX Biopharmaceuticals, Inc. ("HanX"), a company focused on development of novel oncology products, for the further development, registration and commercialization in China of ON 123300. This compound has the potential to overcome the limitations of current generation CDK 4/6 inhibitors. Under the terms of the agreement, we will receive an upfront payment, regulatory and commercial milestone payments, as well as royalties on Chinese sales. The key feature of the collaboration is that

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HanX will provide all funding required for Chinese IND enabling studies performed for Chinese Food and Drug Administration IND approval. We and HanX also intend for these studies to comply with the FDA standards. Accordingly, such studies may be used by us for an IND filing with the FDA. We and HanX will oversee the IND enabling studies. We will maintain global rights outside of China.

During 2015 we sold 376,192 shares of common stock for net proceeds of $7.5 million. In January 2016, we completed a sale of common stock and warrants for net proceeds of approximately $1.6 million. In July 2016, we completed a rights offering of units of common stock and warrants for net proceeds of $15.8 million. In December 2016, we entered into a sales agreement with FBR Capital Markets & Co. ("FBR") to create an at-the-market equity program under which we from time to time may offer and sell shares of common stock through FBR. Sales under this sales agreement in 2017 were 20,499 shares for net proceeds of approximately $64,000. The sales agreement was terminated effective April 19, 2017. There were no sales of common stock under this program during the year ended December 31, 2016.

In April 2017, we closed on an underwritten public offering of 2,476,190 shares of Common Stock. In May 2017, we sold an additional 363,580 shares as a result of the underwriter's exercise of its over-allotment option. Net proceeds from these transactions were approximately $5.3 million. In November 2017, we closed on a registered direct offering to select accredited investors of 920,000 shares of common stock. Net proceeds were approximately $1.1 million. In February 2018, we closed on an offering of units of common stock and warrants. We issued 7,005,000 shares of common stock, pre-funded warrants to purchase 2,942,500 share of common stock, and preferred stock warrants to purchase 1,044,487.5 shares of Series A convertible preferred stock. Each share of Series A convertible preferred stock is convertible into ten shares of common stock. Net proceeds were approximately $8.7 million.

Our net losses were $24.1 million and $19.7 million for the years ended December 31, 2017 and 2016, respectively. As of December 31, 2017, we had an accumulated deficit of $362.3 million. We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, and seek regulatory approval for, our product candidates, even if milestones under our license and collaboration agreements may be met.

As of December 31, 2017, we had $4.0 million in cash and cash equivalents. We believe that our cash and cash equivalents will be sufficient to fund our ongoing trials and operations into the third quarter of 2018, although there is substantial doubt about our ability to continue as a going concern. See " Liquidity and Capital Resources Operating and Capital Expenditure Requirements."

Subsequent to December 31, 2017, in March 2018, we entered into a license agreement with Pint granting an exclusive, royalty-bearing license for the development and commercialization of rigosertib in South and Central America. Pint has agreed to make an upfront equity investment and a subsequent equity investment in our common stock. In addition, we could receive up to $42.75 million in additional regulatory, development and sales-based milestone payments as well as tiered, double digit royalties based on net aggregate net sales in the Territory. Pint also has agreed to purchase rigosertib and the Product exclusively from us in accordance with a supply and quality agreement between the parties. Pint may terminate the License Agreement in whole (but not in part) at any time upon 45 days' prior written notice. The License Agreement also contains customary provisions for termination by either party in the event of breach of the License Agreement by the other party, subject to a cure period, or bankruptcy of the other party.

On February 28, 2018, we filed a definitive proxy statement with the Securities and Exchange Commission relating to a Special Meeting of Stockholders we intend to hold on March 21, 2018 to seek stockholders' approval to increase the number of authorized shares of capital stock from 30,000,000 shares to 105,000,000 shares in order to increase the number of authorized shares of common stock from 25,000,000 shares to 100,000,000 shares.

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Financial Overview

Revenue

During the years ended December 31, 2017 and 2016, our revenues were derived exclusively from activities conducted in accordance with our collaboration arrangements with Baxalta and SymBio. The following table sets forth a summary of revenue recognized during the years ended December 31, 2017 and 2016:

	Year ended December 31,	
	2017	2016
Baxalta	$	$ 4,999,000
SymBio	787,000	547,000
	$ 787,000	$ 5,546,000

We have not generated any revenue from commercial product sales. In the future, if any of our product candidates currently under development are approved for commercial sale in the United States or other territories where we have retained commercialization rights, we may generate revenue from product sales, or alternatively, we may choose to select a collaborator to commercialize our product candidates in these markets.

The Baxalta collaboration agreement was considered to be a multiple-element arrangement for accounting purposes. We determined that there were two deliverables under the Baxalta agreement; specifically, the license to rigosertib for Europe and the related research and development services that we were obligated to provide. We concluded that $42.4 million of the fixed and determinable $50.0 million upfront payment was associated with the license and $7.6 million was associated with the research and development services. We recognized the entire $42.4 million associated with the upfront license as revenue during the third quarter of 2012 upon the execution of the Baxalta agreement, and we recognized the research and development services revenue of $7.6 million on the proportional performance method over the period of commitment and development, which was estimated to be through March 31, 2014, the period of our non-contingent obligations to perform research and development services sufficient to advance rigosertib. In accordance with the agreement, we elected to have Baxalta fund fifty percent of the costs of the INSPIRE trial, up to $15.0 million. For the years ended December 31, 2017 and 2016, we recognized $0.0 million and $5.0 million, respectively, of research and development services revenue related to Baxalta's funding of the INSPIRE trial. On March 3, 2016, we received notification of Baxalta's election to terminate the development and license agreement based on a strategic reprioritization review, effective August 30, 2016, at which time, the rights licensed to Baxalta reverted to us at no cost. Additionally, any rights we had to funding, pre-commercial milestone payments and royalties from Baxalta terminated in accordance with the agreement.

The SymBio collaboration agreement is also considered to be a multiple-element arrangement for accounting purposes. We determined that there were three deliverables under the SymBio collaboration agreement; specifically, the license to rigosertib for Japan and Korea, our obligation to perform research and development services necessary for SymBio to seek approval in its territory and our obligation to participate on a joint steering committee. We concluded that these deliverables should be accounted for as a single unit of accounting. We determined that the $7.5 million upfront payment received in 2011 should be deferred and recognized as revenue on a straight-line basis through December 2027, reflecting our estimate of when we will complete our obligations under the agreement. For the years ended December 31, 2017 and 2016, we recognized revenues of $454,000 and $455,000, respectively, under the SymBio collaboration agreement. In addition, we recognized revenues of

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$333,000 and $92,000 for the years ended December 31, 2017 and 2016, respectively, related to the supply agreement with SymBio.

Operating Expenses

The following table summarizes our operating expenses for the years ended December 31, 2017 and 2016:

	2017	2016
General and administrative	$ 7,405,000	$ 9,178,000
Research and development	19,119,000	20,071,000
Total operating expenses	$ 26,524,000	$ 29,249,000

General and Administrative Expenses

General and administrative expenses consist principally of salaries and related costs for executive and other administrative personnel, including stock-based compensation and travel expenses. Other general and administrative expenses include facility-related costs, communication expenses, insurance, board of directors expenses and professional fees for legal, patent review, consulting and accounting services.

We anticipate that our general and administrative expenses will remain consistent in the short-term, but would increase in the future with the continued research and development and potential commercialization of our product candidates. These increases will likely include increased costs for insurance, costs related to the hiring of additional personnel and payments to outside consultants among other expenses. Additionally, if and when we believe a regulatory approval of a product candidate appears likely, we anticipate an increase in payroll and expense as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidates.

Research and Development Expenses

Our research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with CROs and investigative sites that conduct our clinical trials and preclinical studies;
- the cost of acquiring, developing and manufacturing clinical trial materials;
- direct expenses for maintenance of research equipment, clinical trial insurance and other supplies; and
- costs associated with preclinical activities and regulatory operations.

Research and development costs are expensed as incurred. License fees and milestone payments we make related to in-licensed products and technology are expensed if it is determined that they have no alternative future use. We record costs for some development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or information provided to us by our vendors.

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Research and development activities are central to our business model. Product 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 our research and development expenses to increase in the short-term as the number of sites and enrolled patients related to our INSPIRE clinical trial increases.

To date, our research and development expenses have related primarily to the development of rigosertib. We do not currently utilize a formal time allocation system to capture expenses on a project-by-project basis because we are organized and record expense by functional department and our employees may allocate time to more than one development project. Accordingly, we do not allocate expenses to individual projects or product candidates, although we do allocate some portion of our research and development expenses by functional area and by compound.

The following table summarizes our research and development expenses by functional area for the years ended December 31, 2017 and 2016:

	Year ended December 31,	
	2017	**2016**
Pre-clinical & clinical development	$ 10,660,000	$ 8,513,000
Personnel related	4,244,000	6,149,000
Manufacturing, formulation & development	1,340,000	1,490,000
Stock-based compensation	735,000	2,042,000
Consulting fees	2,141,000	1,877,000
	$ 19,119,000	$ 20,071,000

It is difficult to determine with certainty the duration and completion costs of our current or future preclinical programs and clinical trials of our product candidates, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of future clinical and preclinical studies, uncertainties in clinical trial enrollment rate and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, an assessment of each product candidate's commercial potential and our available funds.

Interest Expense and Other Income, Net

Other income, net consists principally of interest income earned on cash and cash equivalent balances and foreign exchange gains and losses.

Critical Accounting Policies and Significant Judgments and Estimates

This management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses, revenue recognition, deferred revenue and stock-based compensation. We base our estimates on historical experience, known trends

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and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values 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 the notes to our consolidated financial statements appearing elsewhere in this Annual Report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Revenue Recognition

We generate revenue primarily through collaborative research and license agreements. The terms of these agreements contain multiple deliverables, which may include licenses, research and development activities, participation in joint steering committees and product supply. The terms of these agreements may include nonrefundable upfront license fees, payments for research and development activities, payments based upon the achievement of specified milestones, royalty payments based on product sales derived from the collaboration, and payments for supplying product. In all instances, we recognize revenue only when the price is fixed or determinable, persuasive evidence of an arrangement exists, delivery has occurred or the services have been rendered, collectability of the resulting receivable is reasonably assured and we have fulfilled our performance obligations under the contract.

Effective January 1, 2011, we adopted the Financial Accounting Standards Board, or FASB, Accounting Standards Update, or ASU, No. 2009-13, *Multiple-Deliverable Revenue Arrangements* , or ASU 2009-13. This guidance, which applies to multiple-element arrangements entered into or materially modified on or after January 1, 2011, amends the criteria for separating and allocating consideration in a multiple-element arrangement by modifying the fair value requirements for revenue recognition and eliminating the use of the residual value method. The selling prices of deliverables under an arrangement may be derived using third-party evidence, or TPE, or a best estimate of selling price, or BESP, if vendor-specific objective evidence of fair value, or VSOE, is not available. The objective of BESP is to determine the price at which we would transact a sale if the element within the license agreement was sold on a standalone basis. Establishing BESP involves management's judgment and takes into account multiple factors, including market conditions and company-specific factors, such as those factors contemplated in negotiating the agreements as well as internally developed models that include assumptions related to market opportunity, discounted cash flows, estimated development costs, probability of success, and the time needed to commercialize a product candidate pursuant to the license. In validating the BESP, management considers whether changes in key assumptions used to determine the BESP will have a significant effect on the allocation of the arrangement consideration between the multiple deliverables. We may use third-party valuation specialists to assist us in determining BESP. Deliverables under the arrangement are separate units of accounting if (i) the delivered item has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially within our control. The arrangement consideration that is fixed or determinable at the inception of the arrangement is allocated to the separate units of accounting based on their relative selling prices. The appropriate revenue recognition model is applied to each element and revenue is accordingly recognized as each element is delivered. Management exercises significant judgment in determining whether a deliverable is a separate unit of accounting.

In determining the separate units of accounting, we evaluate whether the license has standalone value to the collaborator based on consideration of the relevant facts and circumstances for each arrangement. Factors considered in this determination include the research and development capabilities of the collaborator and the availability of relevant research expertise in the marketplace. In

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addition, we consider whether or not (i) the collaborator can use the license for its intended purpose without the receipt of the remaining deliverables, (ii) the value of the license is dependent on the undelivered items and (iii) the collaborator or other vendors can provide the undelivered items.

Under a collaborative research and license agreement, a steering committee is typically responsible for overseeing the general working relationships, determining the protocols to be followed in the research and development performed, and evaluating the results from the continued development of the product. We evaluate whether our participation in joint steering committees is a substantive obligation or whether the services are considered inconsequential or perfunctory. The factors we consider in determining if our participation in a joint steering committee is a substantive obligation include: (i) which party negotiated or requested the steering committee, (ii) how frequently the steering committee meets, (iii) whether or not there are any penalties or other recourse if we do not attend the steering committee meetings, (iv) which party has decision making authority on the steering committee and (v) whether or not the collaborator has the requisite experience and expertise associated with the research and development of the licensed intellectual property.

For all periods presented, whenever we determine that an element is delivered over a period of time, we recognize revenue using either a proportional performance model or a straight-line model over the period of performance, which is typically the research and development term. We typically use progress achieved under our various CRO contracts as the measure of performance. At each reporting period, we reassess our cumulative measure of performance and make appropriate adjustments, if necessary. We recognize revenue using the proportional performance model whenever we can make reasonably reliable estimates of the level of effort required to complete our performance obligations under an arrangement. We recognize revenue under the proportional performance model at each reporting period by multiplying the total expected payments under the contract, excluding royalties and payments contingent upon achievement of milestones, by the ratio of the level of effort incurred to date to the estimated total level of effort required to complete the performance obligations under the arrangement. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the proportional performance model as of each reporting period. Alternatively, if we cannot make reasonably reliable estimates of the level of effort required to complete our performance obligations under an arrangement, then we recognize revenue under the arrangement on a straight-line basis over the period expected to complete our performance obligations.

Incentive milestone payments may be triggered either by the results of our research efforts or by events external to us, such as regulatory approval to market a product. We recognize consideration that is contingent upon achievement of a milestone in its entirety as revenue in the period in which the milestone is achieved, but only if the consideration earned from the achievement of a milestone meets all the criteria for the milestone to be considered substantive at the inception of the arrangement. For a milestone to be considered substantive, the consideration earned by achieving the milestone must be commensurate with either our performance to achieve the milestone or the enhancement of the value of the item delivered as a result of a specific outcome resulting from our performance to achieve the milestone, relate solely to our past performance and be reasonable relative to all deliverables and payment terms in the collaboration agreement.

For events for which the occurrences are contingent solely upon the passage of time or are the result of performance by a third party, we will recognize the contingent payments as revenue when payments are earned, the amounts are fixed and determinable and collectability is reasonably assured.

We will recognize royalty revenue, if any, as earned in accordance with the contract terms when third-party sales can be reliably measured and collectability is reasonably assured.

We recognized revenue of $0.0 million and $5.0 million during the years ended December 31, 2017 and 2016, respectively, under our license and collaboration agreement with Baxalta. We recognized

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revenue of $0.8 million and $0.5 million during the years ended December 31, 2017 and 2016, respectively, under our license and collaboration agreement with SymBio.The Baxalta and SymBio agreements are being accounted for under ASU 2009-13.

Research and Development Expenses

Research and development costs are charged to expense as incurred and include, but are not limited to, license fees related to the acquisition of in-licensed products, employee-related expenses, including salaries, benefits and travel, expenses incurred under agreements with CROs and investigative sites that conduct clinical trials and preclinical studies, the cost of acquiring, developing and manufacturing clinical trial materials, facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies and costs associated with preclinical activities and regulatory operations.

We record costs for certain development activities, such as clinical trials, based on our evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, or information provided to us by our vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid or accrued research and development expense, as the case may be.

Income Taxes

We recorded deferred tax assets of $144.4 million as of December 31, 2017, which have been fully offset by a valuation allowance due to uncertainties surrounding our ability to realize these tax benefits. The deferred tax assets are primarily composed of federal and state tax net operating loss ("NOL"), carry forwards and research and development tax credit carry forwards. As of December 31, 2017, we had federal NOL carry forwards of $210.5 million, state NOL carry forwards of $169.7 million, and research and development tax credit carry forwards of $79.7 million available to reduce future taxable income, if any. These federal NOL carry forwards will begin to expire at various dates starting in 2022. The state NOL carry forwards will begin to expire at various dates starting in 2025. In general, if we experience a greater than 50 percentage point aggregate change in ownership of specified significant stockholders over a three-year period, utilization of our pre-change NOL carry forwards will be subject to an annual limitation under Section 382 of the U.S. Internal Revenue Code of 1986, as amended (the "Code") and similar state laws. Such limitations may result in expiration of a portion of the NOL carry forwards before utilization and may be substantial. The amount of the annual limitation, if any, will be 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.

Stock-Based Compensation

Prior to April 2013, our stock option awards were accounted for as liability awards as we, through our chairman of the board of directors, who is also a significant stockholder, had established a pattern of settling these awards for cash. Accordingly, we measured stock-based compensation expense at the end of each reporting period based on the intrinsic value of all outstanding vested stock options on each reporting date and recognized expense based on any increases in their intrinsic value since the last measurement date to the extent the stock options vested. The intrinsic value represented the difference between the current fair value of our common stock and the contractual exercise prices of the awards.

On April 23, 2013, we distributed a notification letter to all holders of stock options under our 2007 Equity Compensation Plan advising them that cash settlement transactions would no longer occur, unless, at the time of a cash settlement transaction, the option holder has held the common stock issued upon exercise of options for a period of greater than six months prior to such cash settlement

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transaction and that any such settlement would be at the fair value of the common stock on the date of such sale. Following this notification, we reclassified options outstanding under our 2007 Equity Compensation Plan from liabilities to stockholders' deficit within our consolidated balance sheets. Upon issuing the notification, a modification to the liability awards occurred and the awards are now accounted for as equity awards from the date of modification with compensation expense fixed at fair value at the modification date. As a result, we reclassified the amount of stock-based compensation liability at the modification date to additional paid-in capital. The modification date fair value is recognized over the remaining service period, generally the vesting period, on a straight-line basis. The fair value of the modified awards was estimated on the modification date using the intrinsic value model. The grant date fair value of awards granted after the modification is estimated using the Black-Scholes valuation model, net of estimated forfeitures. Awards granted to non-employees will also be valued using the Black-Scholes valuation model and will be subject to periodic adjustment until the underlying equity instruments vest.

We record stock-based compensation expense as a component of research and development expenses or general and administrative expenses, depending on the function performed by the optionee. For the years ended December 31, 2017 and 2016, we allocated stock-based compensation as follows:

	Year ended December 31,	
	2017	**2016**
General and administrative	$ 975,000	$ 1,887,000
Research and development	735,000	2,042,000
	$ 1,710,000	$ 3,929,000

Fair Value Estimates

Since April 23, 2013, we estimate the fair value of share-based awards to employees and directors using the Black-Scholes option pricing model. The Black-Scholes model requires the input of highly complex and subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of the expected term of the award, (c) the risk free interest rate and (d) expected dividends. Expected volatility is based on the historical volatility of the Company's common stock since its IPO in July 2013. We estimate the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the arithmetic average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. We have never paid, and do not expect to pay dividends in the foreseeable future.

Warrants

Common stock warrants are accounted for in accordance with applicable accounting guidance provided in ASC Topic 815, *Derivatives and Hedging Contracts in Entity's Own Equity* (ASC Topic 815), as either derivative liabilities or as equity instruments depending on the specific terms of the warrant agreement. Some of our warrants are classified as liabilities because in certain circumstances they could require cash settlement. We estimate the fair value of warrants accounted for as liabilities using market quotes from an active and orderly market when available or the Black-Scholes pricing model when quotes are not available.

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Warrants outstanding and warrant activity for the year ended December 31, 2017 is as follows:

Description	Classification	Exercise Price	Expiration Date	Balance Decemeber 31, 2016	Warrants Issued	Warrants Exercised	Warrants Expired	Balance December 31, 2017
Non-tradable warrants	Liability	$ 11.50	July 2021	96,842				96,842
Tradable warrants	Liability	$ 4.92	July 2021	3,192,022				3,192,022
Non-tradable pre-funded warrants	Equity	$ 0.01	July 2023	236,907		(231,000)		5,907
				3,525,771		(231,000)		3,294,771

The following table presents a reconciliation of the fair value of our warrant liability for the years ended December 31, 2017 and 2016:

	Warrant Liability
Balance at December 31, 2015	$
Issuance of warrants	7,389,000
Change in fair value upon re-measurement	(3,988,000)
Balance at December 31, 2016	$ 3,401,000
Change in fair value upon re-measurement	(1,628,000)
Balance at December 31, 2017	$ 1,773,000

Clinical Trial Expense

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. Our clinical trial accrual process is designed to account for expenses resulting from our obligations under contracts with vendors, consultants and CROs and clinical site agreements in connection with conducting clinical trials. The financial terms of these contracts are subject to negotiations, which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided to us under such contracts. Our objective is to reflect the appropriate clinical trial expenses in our consolidated financial statements by matching the appropriate expenses with the period in which services are provided and efforts are expended. We account for these expenses according to the progress of the trial as measured by patient progression and the timing of various aspects of the trial. We determine accrual estimates through financial models that take into account discussion with applicable personnel and outside service providers as to the progress or state of completion of trials, or the services completed. During the course of a clinical trial, we adjust our clinical expense recognition if actual results differ from our estimates. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on the facts and circumstances known to us at that time. Our clinical trial accrual and prepaid assets are dependent, in part, upon the receipt of timely and accurate reporting from CROs and other third-party vendors. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low for any particular period.

JOBS Act

In April 2012, the JOBS Act was enacted. Section 107 of the JOBS Act provides that an "emerging growth company" can take advantage of an extended transition period for complying with new or revised accounting standards. Thus, an "emerging growth company" can delay the adoption of

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certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other companies.

Results of Operations

Comparison of Years Ended December 31, 2017 and 2016

	Year ended December 31,		
	2017	**2016**	**Change**
Revenue	$ 787,000	$ 5,546,000	$ (4,759,000)
Operating expenses:			
General and administrative	7,405,000	9,178,000	1,773,000
Research and development	19,119,000	20,071,000	952,000
Total operating expenses	26,5324,000	29,249,000	2,725,000
Loss from operations	(25,737,000)	(23,703,000)	(2,034,000)
Change in fair value of warrant liability	1,628,000	3,988,000	(2,360,000)
Other income (expense), net	30,000	62,000	(32,000)
Net loss before income taxes	(24,079,000)	(19,653,000)	(4,426,000)
Income taxes	13,000	14,000	1,000
Net loss	$ (24,092,000)	$ (19,667,000)	$ (4,425,000)

Revenues

Revenues decreased by $4.8 million, or 86%, in 2017 when compared to 2016 primarily as a result of contractual cost-sharing revenue from Baxalta for a portion of the costs of the INSPIRE trial in the 2016 period.

General and administrative expenses

General and administrative expenses decreased by $1.8 million, or 19%, to $7.4 million for the year ended December 31, 2017 compared to $9.2 million for the year ended December 31, 2016. The decrease was primarily caused by a decrease of $0.5 million of severance costs and accelerated stock compensation expense of $0.8 million related to the reduction in force during the 2016 period, as well as lower personnel costs and stock compensation for continuing personnel of $0.2 million. Lower facilities related, insurance, and other general and administrative costs also contributed $0.5 million to the decrease. These decreases were partially offset by higher professional fees of $0.2 million in the 2017 period.

Research and development expenses

Research and development expenses decreased by $1.0 million, or 5%, to $19.1 million for the year ended December 31, 2017 compared to $20.1 million for the year ended December 31, 2016. This decrease was caused primarily by decreases of $1.9 million in personnel costs and $1.2 million of stock compensation expense related to our reduction in workforce in the first quarter of 2016. The decrease was also caused by a reduction of $0.2 million in drug product manufacturing costs. These decreases were partially offset by higher clinical development expense of $2.2 million as a result of our increased spending on INSPIRE and our 09-08 combination expansion study, which commenced during the second quarter of 2017.

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Change in fair value of warrant liability

The fair value of the warrant liability, which relates to warrants issued in January and July 2016, decreased $1.6 million during the year ended December 31, 2017 compared to a decrease of $4.0 million during the year ended December 31, 2016, which resulted in a commensurate decrease in other income during the 2017 period. The fair value of the warrants was estimated using a Black-Scholes methodology during the 2016 period, and in 2017 was based on the quoted market price of the warrants. At December 31, 2017, warrants outstanding entitled the holders to purchase up to 3,294,771 shares of our common stock. These warrants expire in July 2021.

Other income, net

Other income, net, was $30,000 of other income for the year ended December 31, 2017, compared to $62,000 of other income, net for the year ended December 31, 2016. This change of $32,000 was due primarily to $48,000 higher foreign exchange losses in the 2017 period, partially offset by $11,000 higher net interest income and higher other income of $5,000 in the 2017 period.

Liquidity and Capital Resources

Since our inception, we have incurred net losses and generally negative cash flows from our operations. We incurred net losses of $24.1 million and $19.7 million for the years ended December 31, 2017 and 2016, respectively. Since inception our accumulated deficit is $362.3 million. We believe that our cash and cash equivalents will be sufficient to fund our ongoing trials and operations into the third quarter of 2018. Due to our ongoing operating losses and our accumulated deficit, in combination with the fact that the future success of the Company is dependent on its ability to obtain additional financing, the opinion of our independent registered public accounting firm on our audited consolidated financial statements for our fiscal year ended December 31, 2017 contains an explanatory paragraph regarding substantial doubt about our ability to continue as a going concern.

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2017 and 2016:

	Year Ended December 31,	
	2017	**2016**
Net cash (used in) provided by:		
Operating activities	$ (23,820,000)	$ (15,813,000)
Investing activities		
Financing activities	6,360,000	17,423,000
Effect of foreign currency translation	34,000	