Epizyme, Inc.
Form 10-K
March 09, 2016
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2015

or

¨ **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 001-35945

EPIZYME, INC.

(Exact name of registrant as specified in its charter)

Delaware	**26-1349956**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
400 Technology Square, Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	**(Zip code)**

617-229-5872

(Registrant s telephone number, including area code)

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

Common stock, $0.0001 par value	**NASDAQ Global Market**
(Title of each class)	**(Name of exchange on which registered)**

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 x No

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (229.405 of this chapter) 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. x

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

Large accelerated filer ¨	Accelerated filer x
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

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

The aggregate market value of the registrant s common stock, par value $0.0001 per share, held by non-affiliates of the registrant on June 30, 2015, the last business day of the registrant s most recently completed second fiscal quarter, was approximately $609.8 million based on the closing price of the registrant s common stock on the NASDAQ Global Market on that date.

The number of outstanding shares of the registrant s common stock, par value $0.0001 per share, as of March 1, 2016 was 57,209,270.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement that the registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant s 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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Annual Report on Form 10-K for the Fiscal Year Ended December 31, 2015

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Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. These statements may be identified by such forward-looking terminology as anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s statements or variations of such terms. Our forward-looking statements are based on a series of expectations, assumptions, estimates and projections about our company, are not guarantees of future results or performance and involve substantial risks and uncertainty. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. Our business and our forward-looking statements involve substantial known and unknown risks and uncertainties, including the risks and uncertainties inherent in our statements regarding:

- our plans to develop and commercialize novel epigenetic therapies for cancer patients;
- our ongoing and planned clinical trials, including the timing of initiation and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;
- our ability to receive research funding and achieve anticipated milestones under our collaborations;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of our products;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

All of our forward-looking statements are as of the date of this Annual Report on Form 10-K only. In each case, actual results may differ materially from such forward-looking information. We can give no assurance that such expectations or forward-looking statements will prove to be correct. An occurrence of or any material adverse change in one or more of the risk factors or risks and uncertainties referred to in this Annual Report on Form 10-K or included in our other public disclosures or our other periodic reports or other documents or filings filed with or furnished to the Securities and Exchange Commission, or the SEC, could materially and adversely affect our business, prospects, financial condition and results of operations. Except as required by law, we do not undertake or plan to update or revise any such forward-looking statements to reflect actual results, changes in plans, assumptions, estimates or projections or other circumstances affecting such forward-looking statements occurring after the date of this Annual Report on Form 10-K, even if such results, changes or circumstances make it clear that any forward-looking

information will not be realized. Any public statements or disclosures by us following this Annual Report on Form 10-K which modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K.

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PART I

Item 1. Business

Overview

Epizyme is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for cancer patients. We are leaders in discovering and developing small molecule inhibitors of a class of enzymes known as histone methyltransferases, or HMTs. We are also expanding our development efforts beyond HMTs and are developing small molecule inhibitors of other chromatin modifying proteins, or CMPs. CMPs mediate selective and reversible modifications to chromatin, a complex of chromosomal DNA and histone proteins that controls gene expression. This chromatin remodeling and its resultant control of gene expression are part of a larger regulatory system, commonly referred to as epigenetics. Genetic alterations within CMPs or that indirectly affect CMPs can result in changes to their activity and drive multiple types of cancer, including hematological cancers and solid tumors. We believe that inhibiting altered CMPs presents the opportunity to create, develop and commercialize multiple targeted therapeutics.

Our lead product candidate, tazemetostat, is a potent and selective inhibitor of the EZH2 HMT, an enzyme that plays an important role in various cancers. In our ongoing phase 1 clinical trial of tazemetostat in patients with relapsed or refractory non-Hodgkin lymphoma, or NHL, or in patients with advanced solid tumors, tazemetostat has shown meaningful clinical activity as a monotherapy, with an acceptable safety profile, in both NHL and in certain genetically-defined solid tumors. We are currently evaluating tazemetostat in a phase 2 study in adults with relapsed or refractory NHL, and one phase 2 study in adults and one phase 1 study in children with certain genetically-defined solid tumors. In addition, in mid-2016, we plan to initiate clinical trials of tazemetostat in combination with other therapies being used or investigated for the treatment of NHL. The first of these studies will test tazemetostat in combination with R-CHOP, the standard of care front-line combination treatment for diffuse large B-cell lymphoma, or DLBCL, an aggressive form of NHL, in front line elderly patients with DLBCL. We plan to initiate this study in the second quarter of 2016. The second of these studies will be conducted in patients with relapsed or refractory DLBCL, and will test tazemetostat in combination with either an anti-PD1 antibody or an anti-PDL1 antibody, which represent an important emerging class of biologic therapies and therapeutic candidates that enhance the body s immune response to cancer, and are commonly referred to as checkpoint inhibitors. We plan to enter into an arrangement with a collaboration partner for this study in the second quarter of 2016 and to initiate this study in mid-2016. In addition, we plan to initiate in the third quarter of 2016 a phase 2 study of tazemetostat in patients with mesothelioma characterized by loss-of-function of BAP1, an enzyme involved in EZH2 regulation. We are continuing to explore in preclinical testing other tumor types that may be sensitive to tazemetostat.

We own the global development and commercialization rights to tazemetostat outside of Japan. Eisai Co. Ltd, or Eisai, holds the rights to develop and commercialize tazemetostat in Japan, and holds a limited right of first negotiation for the rest of Asia. Tazemetostat is protected by U.S. composition of matter patents, which are expected to expire in 2032. In February 2016, tazemetostat was granted orphan drug designation by the FDA for the treatment of malignant rhabdoid tumors, or MRT. The orphan drug designation applies to INI1-negative MRT as well as SMARCA4-negative malignant rhabdoid tumor of the ovary, or MRTO, also known as small cell carcinoma of the ovary hypercalcemic type, or SCCOHT.

We have several additional programs in development, including a phase 1 clinical trial of pinometostat, an inhibitor of the DOT1L HMT, for the treatment of children with MLL-r, an acute leukemia with genetic alterations of the MLL gene. Under our collaboration with Celgene Corporation and Celgene RIVOT Ltd., an affiliate of Celgene

Corporation, which we collectively refer to as Celgene, we own commercialization rights to pinometostat in the United States and Celgene owns commercialization rights to pinometostat outside the United States. Along with Celgene, we are also investigating in preclinical studies combinations of pinometostat with other targeted therapies for the treatment of adults with MLL-r.

We have additional small molecule HMT inhibitors that are being developed under our collaborations with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK, and Celgene. Under our collaboration with GSK, GSK

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is developing small molecule inhibitors against three novel HMT targets including protein arginine methyltransferase 5, or PRMT5. We discovered these HMT inhibitors using our proprietary drug discovery platform. GSK has worldwide rights to the inhibitors of the three HMT targets that we delivered to them under the collaboration. Under our collaboration with Celgene, we are developing small molecule inhibitors directed to three other HMT targets in addition to pinometostat. Under the collaboration, we are responsible for all preclinical discovery work as well as phase 1 clinical development for all three targets. Celgene has the option to license worldwide rights to inhibitors directed at two of the three targets, and the option to license ex-U.S. rights to inhibitors directed to the third target. We retain rights to develop and commercialize the third target in the United States. Beyond our two clinical stage programs and the partnered programs with GSK and Celgene, we have also identified five novel epigenetic targets for which we are developing small molecule inhibitors in preclinical drug discovery. We own the global development and commercialization rights to these programs. All of our novel targets have been identified internally using our proprietary drug discovery platform, and all of our small molecule inhibitors have been discovered internally.

Corporate Strategy

Our goal is to become a fully integrated development and commercial oncology company developing novel epigenetic therapies for cancer patients. We have a robust proprietary drug discovery platform and the demonstrated ability to move candidates into clinical development. As we prepare to commercially launch tazemetostat, if approved, we plan to build out the infrastructure necessary to support the successful launch and marketing of this compound. The key elements of our strategy to achieve this goal are to:

Rapidly Advance the Clinical Development of Tazemetostat. We are executing a comprehensive clinical development program of tazemetostat for NHL and certain genetically-defined solid tumors. If we see sufficient evidence of a therapeutic effect in any of these trials, we plan to meet with regulatory authorities to discuss the possibility of an expedited clinical development and regulatory pathway for the applicable program. If sufficiently safe and active in the target patient populations, we believe that tazemetostat may be able to rely on an expedited regulatory approval process.

Seek to Expand the Range of Potential Indications for Tazemetostat. The R-CHOP combination study we are pursuing is designed to investigate the utility of tazemetostat in front line DLBCL, which would expand the potential commercial opportunity for tazemetostat. We also have over two dozen academic collaborations which are investigating the role of tazemetostat in other cancer types in preclinical models. If we see strong preclinical evidence of sensitivity of specific tumors to EZH2 inhibition, and if a medical need exists, we will consider initiating proof of concept human clinical trials.

Establish Commercialization and Marketing Capabilities in the United States. We have retained commercialization rights in the United States for all of our programs, other than the three programs that are the subject of our GSK collaboration and two of the programs that are the subject of our collaboration with Celgene. We plan to retain commercialization rights in the United States and possibly selected foreign jurisdictions in connection with any future oncology collaborations. We intend to build a focused specialty sales force and marketing capabilities to commercialize any of our oncology drugs that receive regulatory approval in the United States, and the capability of leading global commercial strategy.

Use Our Drug Discovery Platform to Build a Pipeline of Proprietary CMP Inhibitors. Using our proprietary drug discovery platform, we are developing additional novel, small molecule inhibitors of CMPs involved in cancer. We currently hold U.S. development and commercialization rights to one of our three preclinical programs subject to Celgene s option under our collaboration. In addition, we have identified five novel CMP targets against which we are developing small molecule inhibitors in preclinical drug discovery, for which we own all development and commercialization rights.

Leverage Collaborations. Our therapeutic collaborations with Celgene, GSK and Eisai provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our

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collaborators. Our collaborations with Celgene and GSK potentially provide us with significant funding for both our specific development programs and our product platform. We believe that collaborations like these can contribute to our ability to rapidly advance our product candidates, build our product platform and concurrently progress a wide range of discovery and development programs, and may seek to enter into additional therapeutic collaborations in the future.

Develop Companion Diagnostics for Use with Our Therapeutic Product Candidates. We plan to seek to develop companion diagnostics for use in connection with our therapeutic product candidates where appropriate. We believe that this approach may enable us to accelerate the clinical development and regulatory timelines for our therapeutic product candidates and, for any of our therapeutic product candidates that receive marketing approval, improve patient care by identifying patients who are more likely to benefit from the therapy. We intend to develop diagnostics based on currently available diagnostic technologies to the extent possible in order to minimize development and regulatory risk of our diagnostic programs. We are working with Roche Molecular Systems, Inc., or Roche, to develop a companion diagnostic, based on currently available technology, for use with tazemetostat for NHL patients with EZH2 point mutations and are relying on existing laboratory tests for use with pinometostat to identify MLL-r patients. We also plan to develop a companion diagnostic to identify patients with BAP1 loss-of-function for our mesothelioma program.

Background

Cancer is a heterogeneous group of diseases characterized by uncontrolled cell division and growth. Cancerous cells that arise in the lymphatic system and bone marrow are referred to as hematological tumors. Cancer cells that arise in other tissues or organs are referred to as solid tumors. Researchers believe that exposure to some chemicals, viruses and various forms of radiation can cause genetic alterations that cause cancer. Genetic predispositions also can increase the risk of cancer in some people.

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. The American Cancer Society estimated that in 2016 there will be approximately 1.7 million new cases of cancer and approximately 596,000 deaths from cancer in the United States.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. The goal of drug therapy is to damage and kill cancer cells or to interfere with the molecular and cellular processes that control the development, growth and survival of cancer cells. In many cases, drug therapy entails the administration of several different drugs in combination. Over the past several decades, drug therapy has evolved from non-specific drugs that kill both healthy and cancerous cells, to drugs that target specific molecular pathways involved in cancer and more recently to therapeutics that target the specific oncogenic drivers of cancer.

Cytotoxic Chemotherapies. The earliest approach to pharmacological cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. These drugs include Cytosar-U and Cytoxan. While these drugs have been effective in the treatment of some cancers, many unmet medical needs for the treatment of cancer remain. Also, cytotoxic drug therapies act in an indiscriminate manner, killing healthy as well as cancerous cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not

effective in eradicating cancer cells.

Targeted Therapies. Another approach to pharmacological cancer treatment was to develop drugs, referred to as targeted therapeutics, that target specific biological molecules in the human body that play a role in rapid cell

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growth and the spread of cancer. Targeted therapeutics include vascular disruptors, also referred to as angiogenesis inhibitors, that prevent the formation of new blood vessels and restrict a tumor s blood supply. Marketed vascular disruptors include Avastin and Zaltrap. Other targeted therapies, such as Herceptin and Tarceva, affect cellular signaling pathways that are critical for the growth of cancer. These drugs focus on processes that help the cancer cell survive, but not the oncogenes that are the drivers or cause of the cancer itself.

Anti-Oncogenic Therapies. A more recent approach to pharmacological cancer treatment is to develop drugs that affect the drivers that cause uncontrolled growth of cancer cells because of a specific genetic alteration. In some cases, these agents were identified as therapeutics without knowledge of the underlying genetic change causing the disease. To date, the shortcoming of this approach has been that it is not systematic, but instead often follows a conventional trial and error approach to drug discovery. In this approach, clinical development involves the treatment of large populations from which a defined subpopulation that responds to treatment is identified. As a result, this approach can be time-consuming and costly, with success often uncertain.

The Epizyme Approach

We are discovering and developing inhibitors of CMPs as novel precision therapeutics for patients with cancer and other significant unmet medical needs. Our focus is on the discovery, development and eventual commercialization of small molecule inhibitors of CMPs for applications in diseases that are uniquely dependent on the enzyme activity of a specific CMP. Among the CMP target classes, we have a particular emphasis on the HMTs, which have been shown to play pathogenic roles in a number of human diseases. Today, our emphasis is on the development of HMT inhibitors for cancer indications. Beyond cancer, however, HMTs and other CMPs have been implicated as pathogenic drivers of a number of diseases with significant unmet medical need.

Background of Epigenetics and Chromatin Remodeling. Epigenetics refers to a broad regulatory system that controls gene expression without altering the makeup of the genes themselves. Genes are composed of DNA, and in nature, this DNA is wrapped around a core of proteins known as histones. Together, the DNA and histone proteins form a complex known as chromatin that is the basic structural component of chromosomes. The structure of chromatin at specific gene locations can exist either in an open state that permits gene expression or in a more closed state that silences gene expression. The shifting of gene-specific chromatin structure from the open to the closed state, or the closed to open state is referred to as chromatin remodeling. Chromatin remodeling is affected by the reversible placement of small chemical groups acetyl groups, methyl groups and others onto specific sites on the DNA and the histone proteins, in concert with enzyme-catalyzed topographical changes to the contacts between DNA and histones. Some CMPs place these chemical groups onto specific sites on histones or DNA, some remove these marks in site-specific ways, others recognize the uniquely marked sites on histones and bind to these marked sites, and still other CMPs drive topographical changes to histone-DNA interactions within chromatin. Where, when and how such chromatin remodeling reactions occur, determines which genes in a cell are turned on or off at any particular time. When the function of these CMPs is altered, the program of gene expression is changed in ways that often leads to disease.

Cancer and HMTs. We continue to focus the majority of our discovery efforts on the HMT class of CMPs as targets for cancer therapeutics. The HMT class is particularly attractive for drug therapy for several reasons. First, there are a large number of HMTs in humans 96 in total because these enzymes are needed to conduct all of the methylation reactions at distinct locations within the histones. As a result, this class provides a large number of potential drug targets. Second, because HMTs regulate gene expression in a precise fashion, they provide the potential for creation of an inhibitor that can have a desired biological effect. Third, genome discovery efforts have demonstrated that the activity of many of the HMTs is changed due to genetic alterations in cancers in such a way as to make the individual cancers strongly dependent on the enzyme activity of specific HMTs, thereby potentially improving the likelihood that

an inhibitor will have a therapeutic effect.

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While HMTs are a particularly attractive target class of enzymes for drug therapy, in our experience it requires significant effort and scientific knowledge to successfully pursue drug development programs directed at these targets. Key steps in these programs include:

- screening cancer genome sequences specifically to identify alterations directly in HMTs or in related pathways;
- defining an oncogenic hypothesis for the affected HMT;
- developing assays to test the oncogenic hypothesis; and
- creating and optimizing drug-like molecules to inhibit the selected HMT.

Tazemetostat Development Program

Overview. We are developing tazemetostat, a potent and selective inhibitor of the EZH2 HMT, for the treatment of NHL, certain genetically-defined solid tumors and mesothelioma. The following table summarizes our development program for tazemetostat.

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In 2016, we plan to execute on the following clinical development plans for tazemetostat:

- Continue to enroll adult patients into all arms of our ongoing international, registration-supporting five-arm phase 2 study in up to 150 patients with NHL, present interim data from the study at a medical conference in mid-2016 and present a second interim analysis at a medical conference in late 2016;

- Continue to enroll adult patients into all arms of our ongoing international, registration-supporting phase 2 three-arm study in up to 90 patients with certain genetically-defined solid tumors, and present interim data from the study at a medical conference in late 2016;

- Continue to enroll pediatric patients into our ongoing international phase 1 dose escalation and dose expansion study in approximately 40 patients with certain genetically-defined solid tumors;

- Present data from the food effect and drug-drug interaction clinical pharmacology sub-studies of the ongoing phase 1 study in relapsed or refractory NHL or advanced solid tumors at a medical conference in the first half of 2016 and present final data from the phase 1 study in the second half of 2016;

- Initiate a phase 1b/2 study in combination with R-CHOP in front line elderly patients with DLBCL in the first half of 2016;

- Enter into an arrangement with a collaboration partner for a phase 1b study in combination with either an anti-PD1 antibody or an anti-PDL1 antibody in patients with relapsed or refractory DLBCL in the second quarter of 2016 and initiate this study in mid-2016; and

- Initiate a phase 2 study in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function by the third quarter of 2016.

Background on Cancers Characterized by Dysregulation of EZH2. EZH2 is an HMT that can become an oncogenic driver for NHL and a variety of other solid tumors, such as MRT, epithelioid sarcoma and MRTO. As a result, EZH2 has become an important target of oncological drug research.

Non-Hodgkin Lymphoma. Two types of NHL, DLBCL of germinal-center origin and follicular lymphoma, or FL, are associated with oncogenic EZH2 mutations. In our preclinical studies, we observed that NHL cells were sensitive to EZH2 inhibitors such as tazemetostat and that NHL cells bearing EZH2 mutations were particularly responsive to such treatment. EZH2 plays a critical role at various stages in normal B-cell maturation, and a particularly critical role during the stage of B-cell development known as the germinal center reaction. Recent research has demonstrated that EZH2 acts as a critical gatekeeper for B-cell maturation and differentiation. Our own ongoing research suggests that it is a combination of stem like cell-of-origin together with specific genetic lesions that confers sensitivity to EZH2 inhibition to cancer cells. An analysis of patient samples with germinal center derived NHL has revealed a number of genetic alterations that impact EZH2 function in ways that may confer sensitivity to EZH2 inhibition. While DLBCL and FL remain the primary target patient populations for tazemetostat, patients with other forms of NHL may also

benefit from tazemetostat. Other genetic alterations that may impact EZH2 function have been shown to exist in other forms of NHL and in solid tumors. These alterations include amplification of EZH2 and other PRC2 subunit genes, and loss-of-function mutations in histone acetyltransferases, members of the MLL gene family, the SWI/SNF complex and BAP1, and may confer sensitivity to an EZH2 inhibitor.

We estimate the annual incidence rate in the major pharmaceutical markets of DLBCL to be approximately 119,000 patients and the annual incidence rate of FL in the major markets to be approximately 36,000 patients. The 119,000 DLBCL patients include 89,000 patients with activated B-cell and non-germinal-center derived NHL and 30,000 patients with germinal-center DLBCL. We estimate that approximately 6,000 of the germinal-center DLBCL patients carry an EZH2 oncogenic point mutation and that approximately 6,000 of the FL patients carry an EZH2 oncogenic point mutation. Many patients with DLBCL and FL survive beyond the year in which they are diagnosed. Accordingly, we believe that the prevalence of DLBCL and FL in the major pharmaceutical markets is significantly higher than the annual incidence of 155,000 patients. Common treatments for both DLBCL and FL are multi-agent chemotherapy, usually combined with rituximab (Rituxan), including R-CHOP

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and R-ICE and R-DHAP, along with other rituximab containing chemotherapy regimens, which are more often used as salvage regimens following the failure of front line treatment. R-CHOP and R-DHAP are combinations of the cancer agent rituximab, chemotherapy drugs and a steroid; R-ICE is a combination of rituximab and three chemotherapy drugs. Certain patients with DLBCL may also be treated with an allogeneic stem cell transplant.

According to published data from GBI Research, the value of the NHL market in the major developed markets is expected to increase to more than $9 billion by 2020. While current therapies successfully treat more than 50% of DLBCL patients in the front line setting, there remains an unmet medical need in patients who have relapsed or are not responding to treatment. According to a review article published in the 2011 American Society of Hematology Education Book, after standard treatment, approximately one-third of DLBCL patients in a population based registry had refractory disease or had suffered a relapse within a median of four years. FL is generally considered to be incurable with existing therapies.

Genetically- Defined Solid Tumors. INI1 and SMARCA4 are subunits of SWI/SNF, a chromatin modifying protein complex, which opposes the activity of PRC2, the complex within which EZH2 resides. Loss of INI1 or SMARCA4 in specific cell backgrounds is believed to cause dysregulation in the balance between SWI/SNF and PRC2, and thus cause tumors to become sensitive to EZH2 inhibition. This effect was observed in a preclinical study of tazemetostat in a xenograft model of MRT in which tazemetostat caused a dose dependent regression in INI1-negative tumors. INI1-negative tumors can appear in many different tissue types, and can present as MRT, epithelioid sarcoma, extraskeletal myxoid chondrosarcoma, peripheral nerve sheath tumor, myoepithelial carcinoma and renal medullary carcinoma, among several others. SMARCA4-negative tumors can also appear as different tumor types, including MRTO. Synovial sarcoma is characterized by a reciprocal translocation between chromosome 18 and the X chromosome which leads to INI1 dysregulation.

INI1-negative or certain SMARCA4-negative tumors are typically aggressive cancers with few to no treatments approved for these tumors. For example, current treatment of MRT consists of surgery, chemotherapy and radiation therapy, which are associated with limited efficacy and significant treatment-related morbidity in this population. INI1-negative tumors are most commonly seen in infants and toddlers, while SMARCA4-negative tumors and synovial sarcoma are most commonly seen in teenagers and young adults. We believe approximately 3,200 new patients with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma are diagnosed annually in the United States and other major pharmaceutical markets; however, we believe that the actual number may be higher as these types of genetically-defined cancers are significantly under-reported today. MRTO accounts for less than 1% of all ovarian cancer diagnoses, with an average age of 24 years at diagnosis. MRTO is characterized by an aggressive clinical course with two year survival of less than 35%.

Mesothelioma. Mesothelioma is a rare form of cancer that most typically occurs in the lining surrounding the lungs but can also occur in the lining surrounding other organs. Relapsed or refractory mesothelioma remains an unmet medical need. First line treatment typically includes the chemotherapy drugs cisplatin and pemetrexed (Alimta). Median overall survival after standard of care treatment is approximately 13 months. We estimate the total annual incidence of mesothelioma is approximately 12,000 patients in the major pharmaceutical markets. In an article from 2015 in *Pathology*, the authors estimated BAP1 loss-of-function to be associated with approximately 46% of mesothelioma.

Tazemetostat NHL Program. Our ongoing phase 1 study in patients with relapsed or refractory NHL or in patients with advanced solid tumors is being conducted in France, the United Kingdom and Australia. We have completed enrollment in the study with 64 patients. The phase 1 study is comprised of a dose escalation study, a dose expansion study, and two clinical pharmacology studies: a food effect study and a drug-drug interaction study. Interim results from the phase 1 study, including efficacy results for the solid tumor patients, were reported at the European Cancer

Congress 2015, or ECC, in Vienna, Austria, on September 26, 2015, and subsequent interim results from the phase 1 study, including efficacy results for the NHL patients, were reported at the 57th American Society of Hematology Annual Meeting, or ASH, in Orlando, Florida, on December 7, 2015.

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The primary objective of the phase 1 study was to evaluate the safety and tolerability of tazemetostat and to determine the recommended dose for phase 2 trials. In the phase 1 trial, tazemetostat is being administered orally as a monotherapy, twice daily in continuous 28-day cycles. In the dose escalation portion of the study, patients were enrolled in one of five dose cohorts at dose levels of 100, 200, 400, 800, or 1600 mg twice daily. In the dose expansion portion of the study, patients received either 800 or 1600 mg twice daily. In the food effect portion of the study, patients received a single 200 mg dose, with or without food, on the eighth day prior to the start of continuous dosing, a single 200 mg dose, with or without food, one day prior to the start of continuous dosing, and 400 mg twice daily, from the start of the continuous dosing phase.

At ASH, we presented updated data from the phase 1 study, including efficacy data with respect to patients with NHL. All NHL patients were either refractory to or relapsed from prior therapy, which included autologous stem cell transplant in eight of the 21 patients with NHL that were dosed in the study. Of these 21 patients, 18 patients, or 85%, had been treated previously with three or more systemic anti-cancer therapies. As of the November 7, 2015 cutoff date, the following clinical data were reported:

- Twenty-one patients with relapsed or refractory NHL were enrolled into the phase 1 study; 16 of the 21 patients were response-evaluable as defined by the study protocol.

- Tazemetostat showed activity across different subtypes of NHL, including germinal-center and non-germinal center DLBCL and follicular lymphoma, in patients with wild-type EZH2 and mutant EZH2.

- Nine of 16 (56%) response-evaluable NHL patients achieved an objective response.

- On an intent-to-treat basis, seven of 12 (58%) response-evaluable NHL patients treated at or above the recommended phase 2 dose of 800 mg twice daily achieved an objective response.

- Four patients remained on study at data cutoff with ongoing objective responses, including three patients who had been on drug for at least 17 months.

- The 800 mg twice daily dose showed superior tolerability, equivalent anti-tumor activity and equivalent pharmacodynamic activity as compared to the 1600 mg twice daily dose.

- Tazemetostat was well-tolerated. The majority of adverse events were grade 1 or grade 2 within the 55 patients with NHL and solid tumors who were evaluable for safety. The most common adverse events, regardless of attribution, were asthenia, anorexia, thrombocytopenia, nausea, constipation, diarrhea, and vomiting. Four grade 3 or greater treatment-related adverse events have been observed including one each of: grade 3 hypertension, grade 3 liver function test elevation, grade 4 thrombocytopenia, and grade 4 neutropenia.

We are conducting a registration-supporting international 150-patient, five-arm phase 2 clinical trial of tazemetostat for the treatment of NHL. Our five-arm phase 2 NHL study is currently being conducted in five countries including

France, the United Kingdom and Australia. In addition, in December 2015, the U.S. Food and Drug Administration, or FDA, accepted our Investigational New Drug, or IND, application for tazemetostat for DLBCL, which allows us to expand the treatment of DLBCL patients in the study to sites in the United States.

Patients in the phase 2 NHL study are stratified into one of five arms:

- Germinal center DLBCL, wild-type EZH2,
- Germinal center DLBCL, mutant EZH2,
- Non-germinal center DLBCL,
- Follicular lymphoma, wild-type EZH2, and
- Follicular lymphoma, mutant EZH2.

Each of these arms will enroll 30 patients subject to an interim futility analysis for each arm. Overall, enrollment in the five-arm phase 2 NHL study is proceeding as expected. Patients are dosed at 800 mg twice daily with

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tablets taken orally. To date, based on preliminary response data, we believe we have surpassed futility in three of the five arms, and we have not yet achieved the necessary events to determine futility or non-futility in the other two arms. Definitive futility analyses and assessment will be determined at a later date by an independent data safety monitoring committee. We plan to present interim data from the phase 2 five-arm NHL study at a medical conference in mid-2016. The primary endpoint of the study is overall response rate. Secondary endpoints include duration of response, progression free survival, overall survival, safety and population pharmacokinetics.

We have entered into an agreement with Roche for the development of a companion diagnostic for use with tazemetostat for NHL patients with EZH2 point mutations, and are using this diagnostic for the screening of patients in the ongoing phase 2 five-arm NHL study.

Preclinical Studies NHL. Tazemetostat s advancement to the clinic is supported by *in vitro* and *in vivo* activity in both mutant and wildtype EZH2 NHL. In preclinical studies, EZH2 gain-of-function mutations led to oncogenic repression of gene transcription by accelerating trimethylation of the EZH2 substrate H3K27. Consistent with this mechanism, *in vivo* mouse studies demonstrated drug efficacy and durability of response in EZH2-mutant NHL models treated with tazemetostat. Our preclinical studies with wild-type EZH2 lymphoma cells suggest that EZH2 acts as a key regulator of B-cell maturation, and that certain genetic lesions that lead to germinal center lymphomas are also likely to depend on EZH2 activity. This hypothesis is supported by cumulative pre-clinical data with EZH2 inhibitors, and pre-clinical models demonstrating synergy of tazemetostat with B-cell signaling inhibitors.

Tazemetostat Solid Tumor Program. At the ECC, we presented data from our ongoing phase 1 study of tazemetostat in patients with NHL or advanced solid tumors, including efficacy data with respect to patients with solid tumors. As of the data cutoff of August 31, 2015, we had enrolled 30 patients with solid tumors into this ongoing phase 1 study, including eight patients in a food effect sub-study. Of these 30 patients, eight had INI1-negative tumors, comprised of five with MRT and three with epithelioid sarcomas. Additionally, three patients had SMARCA4-negative tumors including two patients with MRTO which is also referred to as small cell carcinoma of the ovary hypercalcemic type, and one patient with thoracic sarcoma. Nineteen patients had other solid tumors that were not characterized by INI1 or SMARCA4 loss, including three patients with synovial sarcomas. More than half of the solid tumor patients were relapsed or refractory and had been treated previously with three or more systemic anti-cancer therapies. As of the August 31, 2015 cutoff date, the following clinical data were reported:

A total of 11 patients with INI1-negative or SMARCA4-negative tumors have been treated. The tumor histology of these patients includes MRT, MRTO, epithelioid sarcoma and thoracic sarcoma. Nine of these 11 patients have been treated at or above the recommended phase 2 dose of 800 mg twice daily.

Six of the 11 patients experienced a reduction in tumor size as best response, with four patients experiencing tumor reduction of over 30%.

Of the five patients with an INI1-negative malignant rhabdoid tumor, one patient achieved a complete response at week eight and had remained on study and in complete response through week 65.

Of three patients with SMARCA4-negative tumors, two patients presented with MRTO. One MRTO patient achieved a partial response at week 8 and had remained on study through week 25. A second MRTO patient

achieved stable disease and had remained on study through week 26.

Of three patients with an INI1-negative epithelioid sarcoma, one patient achieved a partial response of short duration and had remained on study with stable disease through week 25. A second patient had remained on study with stable disease through week 24.

Clinical activity was not observed in the 19 patients with other tumors, including the three patients with synovial sarcomas.

Inhibition of EZH2, as measured by post-treatment H3K27 trimethylation compared to baseline, was observed in tumor tissue of INI1-negative patients as assessed by immunohistochemistry.

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We believe stable disease is a clinically meaningful outcome in this patient population, where in a clinical study of children with rhabdoid tumors, the median survival was less than one year, and in a clinical study of patients with MRTO, the two-year survival rate was less than 35 percent. At the ECC, Dr. Viktor Grünwald, professor at the Medical School of Hanover, Germany, reported data from a cooperative study with The European Organisation for Research and Treatment of Cancer, demonstrating that for the population of patients with soft tissue sarcoma in the study, stable disease was as good a predictor of overall survival as was a composite of partial and complete responses.

Our phase 2 study in adults with certain genetically-defined solid tumors and our phase 1 study in children with certain genetically-defined solid tumors are now enrolling patients in the United States, and we expect to expand enrollment in both studies internationally in 2016.

The adult phase 2 multicenter study in adults with genetically-defined solid tumors will enroll up to 90 patients in three arms.

The first arm will be comprised of patients with MRT, rhabdoid tumor of the kidney and atypical teratoid rhabdoid tumor, all of which are characterized by INI1- or SMARCA4-negativity.

The second arm will be comprised of patients with non-rhabdoid INI1-negative tumors including epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma and renal medullary carcinoma.

The third arm will be comprised of patients with synovial sarcoma.

Patients are dosed at 800 mg twice daily with tablets taken orally. The primary endpoint is overall response rate for patients in the first two cohorts and progression-free survival, or PFS, for patients in the synovial sarcoma cohort. Secondary endpoints include duration of response, overall survival, PFS for patients with INI1-negative tumors, safety and pharmacokinetics. We plan to present interim data from the phase 2 study of tazemetostat in adults with certain genetically-defined solid tumors at a medical conference in late 2016.

The pediatric phase 1 multicenter study in patients with genetically-defined solid tumors will enroll approximately 40 patients in a dose escalation design, followed by dose expansion, with an oral suspension of tazemetostat. The study will enroll patients with the same INI1-negative tumors, SMARCA4-negative tumors or synovial sarcoma as in the phase 2 adult study. The primary endpoint of the study is safety, with the objective of establishing the recommended phase 2 dose in pediatric patients. Secondary endpoints include pharmacokinetics, objective response rate, duration of response, PFS and overall survival.

Tazemetostat has been granted orphan drug designation by the FDA for the treatment of MRT. The orphan drug designation applies to INI1-negative MRT as well as SMARCA4-negative MRTO.

Preclinical Studies Solid Tumors. In addition to genetic alterations in EZH2 itself, distal genetic changes in other proteins can lead to an oncogenic dependency on EZH2 activity. In preclinical *in vitro* and *in vivo* studies tazemetostat has demonstrated utility in the treatment of select INI1-deficient and SMARCA2/A4-deficient tumors, where EZH2 activity is abnormally enhanced due to genetic alterations of the SWItch/Sucrose NonFermentable, or SWI/SNF chromatin remodeling complex. INI1-deficient tumor types include those with complete INI1 deletion. These include extracranial malignant rhabdoid tumor, atypical teratoid rhabdoid tumor, epithelioid sarcomas, epithelioid malignant

peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcoma, renal medullary carcinoma and myoepithelial carcinomas. Additionally, functional INI1 loss by its displacement from the SWI/SNF complex can occur as a result of an oncogenic fusion protein in synovial sarcoma. SMARCA2 and SMARCA4 are, like INI1, additional subunits of the SWI/SNF complex and are deleted in certain solid tumors, including MRTO. In preclinical studies, MRTO cells demonstrated sensitivity to tazemetostat inhibition.

Combination Studies and Other Development Plans. In the first half of 2016, we plan to initiate two trials of tazemetostat in combination with other NHL therapies. The first of these trials will be a phase 1b/2 study in front

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line elderly patients with DLBCL and will combine tazemetostat with R-CHOP. In preclinical models of NHL, tazemetostat showed synergy with R-CHOP, and in particular with the prednisone component. Our second planned combination study in NHL will be a phase 1b study combining tazemetostat with either an anti-PD1 or anti-PDL1 antibody. Reports from various investigators have suggested that EZH2 inhibition sensitizes tumors to checkpoint inhibition, through enhanced exposure of tumor antigens to the immune system and enhanced chemokine signaling to improve trafficking and infiltration of lymphocytes to the tumor microenvironment.

In addition, in preclinical studies, tazemetostat showed synergy with a number of different B-cell signaling agents, including inhibitors of the kinases BTK and PI3K, as well as inhibitors of BCL-2, a regulator of apoptosis, or programmed cell death. In 2016, we will continue to evaluate potential new combination studies with tazemetostat, including with a B-cell signaling agent.

Mesothelioma with EZH2 Disregulation. In the third quarter of 2016, we plan to initiate a phase 2 study of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function.

In preclinical studies of mesothelioma, BAP1 loss-of-function led to increased expression and activity of EZH2. In addition, in animal models of mesothelioma, inhibition of EZH2 by a small molecule inhibited growth of tumor cells in mesothelioma characterized by BAP1 loss-of-function.

Pinometostat DOT1L Inhibitor

Overview. We are developing pinometostat as an intravenously administered small molecule inhibitor of DOT1L for the treatment of acute leukemias with alterations in the MLL gene, specifically rearrangements of MLL as a consequence of chromosomal translocation, referred to as MLL-r, which includes partial tandem duplications of the MLL gene, referred to as MLL-PTD. We invented pinometostat using our proprietary product platform.

In 2014, we initiated a phase 1 trial of pinometostat in pediatric patients with MLL-r. This phase 1 study is enrolling pediatric patients with MLL-r acute leukemia and contains a dose escalation and an expansion cohort that are designed to enable us to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of pinometostat in patients between the ages of three months and 18 years. This trial is also designed to provide a preliminary assessment of efficacy. We intend to complete enrollment in our ongoing phase 1 clinical trial of pinometostat in pediatric MLL-r patients and present preliminary results from this study at a medical conference in the second half of 2016.

In August 2015, we voluntarily ceased patient enrollment in our phase 1 study of pinometostat in adult patients with MLL-r due to insufficient efficacy of pinometostat as a monotherapy. However, we and Celgene are exploring in preclinical studies combinations of pinometostat with other anti-cancer agents to enhance pinometostat s efficacy in the adult MLL-r population. We retain all U.S. rights to pinometostat and have granted Celgene an exclusive license to pinometostat outside of the United States. Pinometostat has been granted orphan drug designation by the FDA and the European Commission for the treatment of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL.

Background on DOT1L Cancers. DOT1L is an HMT that can become oncogenic and cause certain subtypes of acute leukemia, such as MLL-r.

MLL-r is an aggressive, genetically-defined subtype of two of the most common forms of acute leukemia, ALL and AML. In an article in the journal *Blood* in December 2002, the authors estimated that the five-year overall survival rate for adult patients with the MLL-r subtype of AML ranges from approximately 5 to 24%. In an article from 2004 in the *New England Journal of Medicine*, the authors estimated that the five-year event-free survival rate in pediatric

patients with the most common MLL-r subtype of ALL is approximately 27%. We estimate the total annual incidence of MLL-r in pediatric patients in the major pharmaceutical markets to be approximately 1,300 patients. Patients with MLL-r are routinely diagnosed using existing technologies that are commonly used in clinical settings. As a result, there is high awareness of MLL-r among oncologists. The

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disease predominantly occurs in two different age ranges, an adult population and an infant/pediatric population. While they share a common genetic alteration, the adult disease is frequently a secondary leukemia resulting from prior chemotherapy for a different, unrelated cancer and the childhood disease is of unknown origin. MLL-r is caused by a chromosomal translocation involving the MLL gene. The translocation results in DOT1L being recruited to a specific place in the chromosome where it would not normally be present. As a result, DOT1L causes inappropriate histone methylation at this location, which results in the increased expression of genes involved in causing leukemia. There are no approved therapies specifically indicated for MLL-r. Physicians treat this hematological cancer with therapies approved for other acute leukemia. Patients with AML and ALL typically are treated with intensive multi-agent chemotherapy and high risk patients with ALL and AML who enter remission and have a matched donor often receive an allogeneic stem cell transplant.

Other Pipeline Programs

In addition to tazemetostat and pinometostat, we also have a pipeline of small molecule inhibitors in preclinical development that target our other prioritized CMPs. These programs are directed to specific cancers, including both hematological malignancies and solid tumors.

Under our collaboration with GSK, compounds discovered and optimized by us targeting three HMT s, including PRMT5, have been provided to GSK for further development. PRMT5 is reported to have a role in diverse cellular processes, including tumorigenesis. PRMT5 overexpression has been observed in cell lines and primary patient samples derived from a number of cancers, including lymphoma, lung cancer, breast cancer and colorectal cancer. We discovered the HMT inhibitors for the three targets, including PRMT5 under the GSK collaboration using our proprietary drug discovery platform and successfully delivered them to GSK. GSK has worldwide rights to the inhibitors of these three HMT targets

Under our collaboration with Celgene, we are developing small molecule inhibitors directed to three HMT targets, in addition to pinometostat. Under the collaboration, we are responsible for all preclinical discovery work as well as phase 1 clinical development for all three targets. Celgene has the option to acquire worldwide rights to inhibitors directed at two of the three targets, and the option to acquire ex-U.S. rights to inhibitors directed to the third target. We retain rights to develop and commercialize inhibitors directed at the third target in the United States.

In addition to tazemetostat and our partnered programs, we have ongoing drug discovery programs directed to five other novel CMP targets. We own all development and commercialization rights to these five programs.

The Epizyme Discovery Platform

Targeting oncogenic CMPs affords us multiple opportunities to create, develop and commercialize novel, precision therapeutics. To realize the full breadth of this opportunity, we created and continue to expand and enhance our proprietary discovery platform. Our platform aims to optimize the effectiveness of drug discovery and development by creatively addressing four key components of the process:

Judicious Target Selection. Selection of an appropriate target is a critical and challenging aspect of drug discovery. We are meeting the challenges of target selection with a unique combination of novel, optimized approaches to CRISPR technology, proprietary chemical biology methods and cellular and organismal biology approaches that allow us to rigorously and rapidly test targeting hypotheses. Our selection of a target CMP for drug discovery generally requires five critical elements to be satisfied. The target must:

Be a causal driver of pathogenicity and/or represent a unique vulnerability to therapeutic intervention, thus creating a basis for a wide therapeutic index;

Offer a strategy for patient stratification;

Be amenable to inhibition by a small molecule by virtue of the target s molecular structure, and small molecule inhibition of the target must be disease modifying;

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Address a significant unmet medical need for patients; and

Represent a meaningful commercial opportunity.

With respect to the first two of these elements, a common approach in drug discovery is to develop a small molecule drug candidate against a target which itself contains a genetic lesion that causes disease. This is exemplified among the CMPs by gain-of-function mutations within the HMT target EZH2 in subsets of germinal center lymphoma patients. However, through our combined CRISPR, cancer biology and chemical biology approaches, we have also revealed previously unrecognized synthetic lethal relationships affecting CMPs, wherein a genetic lesion that occurs at an unrelated gene product (protein) creates a unique dependency of a disease cell on the enzymatic activity of the CMP. This provides a novel approach to developing small molecule drugs that impact genetic lesions that were generally considered not amenable to drug development. For example, we have observed several cases in which pathogenic loss-of-function genetic lesions at one protein creates a unique reliance of a disease state on the enzymatic activity of a seemingly unrelated CMP, which can then be targeted for small molecule drug therapy. One example of this is the way in which INI deletions render certain cells sensitive to EZH2 inhibition.

Deep Understanding of Target Biochemistry and Biology in the Context of Pathophysiology. Once a target is selected, we invest heavily in understanding the biochemistry and biology of that target in the context of cellular pathophysiology. Knowing how a CMP functions in the cell(s) of interest, details of its catalytic mechanism, which ancillary proteins bind to the target within the cell and impact activity, and its pattern of substrate utilization, all contribute importantly to our ability to create relevant biochemical and cellular assays for compound screening and evaluation.

Comprehensive Molecular Discovery. We take a broad approach to drug discovery that includes an early emphasis on optimization of compounds by evaluating them against multiple criteria. Rather than focusing exclusively on target potency, we evaluate our chemical leads for a spectrum of pharmacological properties at an early point in the drug discovery process. Compounds are simultaneously optimized for target and cellular potency, drug-target residence time, drug metabolism and pharmacokinetics, or DMPK properties, and oral bioavailability. To accomplish this, we integrate a number of molecular science skill bases, together with biological sciences, to form comprehensive matrix discovery teams. These include: medicinal chemistry, enzymology, structural biology, biochemistry and biophysics and preclinical DMPK. We have also applied of comprehensive molecular discovery approach not only to individual targets, but also to target classes, such as the HMTs, through our cross-screening paradigm. In this manner, every compound designed by our chemists is screened against a large collection of representative enzymes of a target class. As a result, we have created a proprietary library of CMP-targeted compounds that today numbers over 32,000 compounds. We have also facilitated drug discovery by solving the co-crystal structures of over 700 CMPs in complex with our small molecule inhibitors. This has allowed us to develop a deep understanding of target class medicinal chemistry and has resulted in the creation of novel chemical starting points for targeted discovery programs.

Early Integration of Preclinical and Clinical Development. We involve our preclinical and clinical teams early in the drug discovery process. We engage our clinicians and translational medicine experts during the target selection process to ensure that informed decisions are being made with respect to our five key elements of target selection. These researchers continue to participate in the program matrix teams to ensure early development of cogent approaches to clinical translation and development. For example, a clear understanding of patient population and their needs with respect to route of administration, dosing form, and dosing schedule, informs team decisions with respect to multi-parametric pharmacological optimization of lead compounds. Likewise, preclinical development expertise in chemistry, manufacturing and controls, or CMC, and safety assessment are engaged early in the discovery process to ensure successful transition of compounds from discovery through clinical evaluation.

We believe that our discovery platform provides us with an important competitive advantage in identifying pathogenic CMPs and creating novel precision therapeutics to treat the diseases caused by these CMPs.

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Collaborations

We have entered into three strategic collaborations for our therapeutic programs. These therapeutic collaborations have provided us with $201.6 million in non-equity funding through December 31, 2015. Our Celgene and GSK collaborations also provide us with development co-funding and the potential for significant research, development, regulatory and sales-based milestone payments as well as royalties or profit sharing on net product sales. In addition, we have entered into a collaboration to develop a companion diagnostic with Roche. Key terms of these collaborations are summarized below.

Celgene

Overview. In July 2015, we entered into an amendment and restatement of our collaboration and license agreement dated April 2012 with Celgene. Under the original agreement, the Company granted Celgene an exclusive license, for all countries other than the United States, to small molecule HMT inhibitors targeting DOT1L, including pinometostat, and an option, on a target-by-target basis, to exclusively license, for all countries other than the United States, rights to small molecule HMT inhibitors targeting any other HMT targets, excluding EZH2 and targets covered by our collaboration and license agreement dated January 8, 2011 with GSK. Under the original agreement, Celgene s option was exercisable during an option period that would have expired in July 2015. Under the amended and restated collaboration and license agreement:

- Celgene retains its exclusive license to small molecule HMT inhibitors targeting DOT1L, including pinometostat,
- Celgene s option rights have been narrowed to HMT inhibitors targeting three predefined targets (the Option Targets),
- The exclusive licenses to HMT inhibitors targeting two of the Option Targets that Celgene may acquire have been expanded to include the United States, with the exclusive license to the third Option Target continuing to be for all countries other than the United States,
- Celgene s option period has been extended for each of the Option Targets and is exercisable at the time of the Company s IND filing for an HMT inhibitor targeting the applicable Option Target, upon the payment by Celgene at such time of a pre-specified development milestone-based license payment,
- Celgene s license may be maintained beyond the end of phase 1 clinical development for each of the Option Targets, upon payment by Celgene at such time of a pre-specified development milestone-based license payment, and
- Our research and development obligations with respect to each Option Target under the amended agreement have been extended for at least an additional three years, subject to Celgene exercising its option with respect to such Option Target at IND filing. Subject to our Opt-Out rights described below, our research and

development obligations have been expanded to include the completion of a phase 1 clinical trial as to each Option Target following Celgene s exercise of its option at IND filing.

To date, we have received $75.0 million of upfront payments (including $10.0 million as part of the amended and restated agreement) and $25.0 million from the sale of our series C preferred stock to an affiliate of Celgene, of which $3.0 million was considered a premium and included as collaboration arrangement consideration for a total upfront payment of $78.0 million. In addition, we received a $25.0 million clinical development milestone payment in 2014 and $6.9 million of global development co-funding through December 31, 2015. In addition, we are eligible to earn up to $75.0 million in development milestones and license payments, up to $365.0 million in regulatory milestone payments and up to $170.0 million in sales milestone payments related to the Option Targets. We remain eligible to earn $35.0 million in an additional clinical development milestone payment and up to $100.0 million in regulatory milestone payments related to DOT1L.

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We are also eligible to receive royalties as follows:

- As to DOT1L, we retain all product rights in the United States and are eligible to receive royalties at defined percentages ranging from the mid-single digits to the mid-teens on annual net product sales outside of the United States, subject to reductions in specified circumstances;

- As to the Option Target for which Celgene s option rights do not include the United States, if Celgene exercises its option as to such Option Target, we will retain all product rights in the United States and will be eligible to receive royalties, once an initial threshold of net product sales (for which we will not receive royalties) is exceeded, at defined percentages ranging from the mid-single digits to the low-double digits on net product sales outside of the United States, subject to reductions in specified circumstances; and

- As to the other two Option Targets, if Celgene exercises its option as to those Option Targets, we will be eligible to receive royalties, once an initial threshold of net product sales (for which we will not receive royalties) is exceeded, for each such Option Target at defined percentages ranging from the mid-single digits to the low-double digits on net product sales on a worldwide basis, subject to reductions in specified circumstances.

For DOT1L and, after Celgene s payment of the specified IND filing license payment for each Option Target, for each such Option Target, we are responsible for the conduct and funding of phase 1 clinical trials, subject to our right to opt-out of such responsibilities as described below. Celgene may obtain a license to small molecule HMT inhibitors targeting each Option Target at the time of the Company s IND filing for an HMT inhibitor for such target by exercising its option and paying us a specified license payment. Celgene may maintain its license with respect to an Option Target at the conclusion of the phase 1 clinical trial of the Option Target by paying us a specified additional license payment. If Celgene does not elect to obtain a license during the option exercise period applicable to an Option Target, or to pay the specified IND license payment or end of phase 1 license payment, we will retain worldwide rights to HMT inhibitors directed to the Option Target, other than HMT inhibitors that may be provided by Celgene if the Company were to agree to their introduction into the collaboration.

Research Obligations. We are primarily responsible for the research strategy under the collaboration. During each applicable option period we are required to use commercially reasonable efforts to carry out an agreed research plan for each Option Target, subject to our Opt-Out right described below. For the DOT1L target and each of the Option Targets, we are required to conduct and solely fund development costs of the phase 1 clinical trials for HMT inhibitors directed to such targets, including for pinometostat. After completion of phase 1 development, as to DOT1L and the Option Target for which we retain U.S. rights, Celgene and the Company will equally co-fund global development and each party will solely fund territory-specific development costs for its territory; and, as to the other two Option Targets, after completion of phase 1 development, Celgene will solely fund all development costs on a worldwide basis.

Governance. Our collaboration with Celgene is guided by (a) a joint research committee, with authority over all activities performed under the research plan with respect to the two Option Targets as to which we granted worldwide rights; (b) a joint development committee, with authority over shared development activities with respect to DOT1L and the Option Target for which we retain U.S. rights; and (c) a joint commercialization committee, with authority over the commercialization of products developed under shared development programs with respect to DOT1L and the Option Target for which we retain U.S. rights. Subject to limitations specified in the amended and restated

agreement, if the applicable governance committee is not able to make a decision by consensus and the parties are not able to resolve the issue through escalation to specified senior executive officers of the parties, then (a) prior to Celgene s exercise of its option, we generally have final decision-making authority over research and development matters with respect to the Option Targets; (b) with respect to DOT1L and any Option Targets for which Celgene has exercised its option, Celgene generally has final decision-making authority over global development matters, including over global activities and related expenses that we are obligated to co-fund, unless we exercise our opt-out right as to such licensed program, and

except that with respect to the Option Target for which we retain U.S. rights, the parties have mutual decision-making authority even after Celgene exercises its option as long as Celgene engages in a competitive development program with respect to such Option Target. Each party has final decision-making authority over commercialization matters in its respective territory.

Opt-Out Right. On an Option Target-by-Option Target basis, we have the right, in our sole discretion, to opt-out of further participation in any research and/or development activities after completion of the initial research plan and prior to the filing of an IND for an HMT inhibitor directed to the applicable Option Target, or the Pre-IND Opt-Out. Following exercise of a Pre-IND Opt-Out, if Celgene exercises its option as to the Option Target, Celgene will no longer be required, to the extent not already paid, to make the specified IND license payment or end of phase 1 license payment to us, specified sales milestone payments will no longer be payable and all royalties on net product sales of applicable licensed products that become payable to us will be reduced by a specified percentage. Additionally, if Celgene exercises its option as to such Option Target, we are obligated to grant Celgene an exclusive worldwide license to HMT inhibitors directed to the applicable Option Target, even if we would otherwise retain U.S. rights to HMT inhibitors directed to the applicable Option Target. Additionally, on a licensed program-by-licensed program basis, we have the right, in our sole discretion, to opt-out of further participation in and co-funding of development, other than specified costs necessary to complete development activities in process at the time we exercise our opt-out right. We can exercise our licensed program opt-out right at specified times: (a) when the clinical trial stopping rules set forth in a clinical trial protocol for DOT1L or the Option Target for which the we retain U.S. rights dictate that such clinical trial be stopped, or the Post-EOP1 Clinical Opt-Out; or (b) for any or no reason, in a licensed program for DOT1L or the Option Target for which we retain U.S. rights, during specified periods before the scheduled initiation of the first pivotal clinical trial or before the estimated date of filing of the first new drug application for an HMT inhibitor directed to the licensed target or any time after regulatory approval of an HMT inhibitor directed to the licensed target, or the Late Stage Opt-Out. In the event of a Post-EOP1 Clinical Opt-Out, the royalties that become payable to us on net product sales of licensed products directed to DOT1L or the Option Target for which we retain U.S. rights, as applicable, will be reduced by a specified percentage. Following a Post-EOP1 Clinical Opt-Out or a Late Stage Opt-Out, we are no longer required to co-fund global development for the applicable program other than specified costs necessary to complete development activities in process at the time we exercises our opt-out right, and we are obligated to grant Celgene an exclusive license to HMT inhibitors directed to the applicable target in the United States. Following our exercise of a Post-EOP1 Clinical Opt-Out or a Late Stage Opt-Out, if any, we would be eligible to receive specified milestone payments and royalties based on net product sales in the United States of HMT inhibitors directed to the licensed target in the event that Celgene develops and commercializes a product in the United States.

Exclusivity Restrictions. Subject to exceptions specified in the amended agreement, during the option period, we may not research, develop or commercialize HMT inhibitors directed to DOT1L and the three Option Targets. Subject to exceptions specified in the amended agreement, following each applicable option period, we may not research, develop or commercialize HMT inhibitors directed to DOT1L or any target licensed by Celgene.

Right of First Negotiation. The amended and restated agreement eliminated the right of first negotiation that we had previously granted to Celgene under the original agreement with respect to business combination transactions that we may desire to pursue with third parties.

Term and Termination. The amended and restated agreement with Celgene will expire on a product-by-product and country-by-country basis on the date of the expiration of the applicable royalty term with respect to each licensed product in each country and in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the latest of expiration of

specified patent coverage, specified regulatory exclusivity or 15 years following the first commercial sale in the applicable country. Celgene has the right to terminate the amended agreement in its entirety, upon 60 or 120 days notice depending on the timing of such termination. The amended agreement may also be terminated in its entirety during the option period, and on a licensed target-by-licensed target basis after

the option period, by either Celgene or the Company in the event of a material breach by the other party. The amended agreement may be terminated on a licensed target-by-licensed target basis by either Celgene or us in the event the other party, or an affiliate or sublicensee of the other party, participates or actively assists in a legal challenge to specified patents of the terminating party or in its entirety in the event the other party becomes subject to specified bankruptcy, insolvency or similar circumstances.

GlaxoSmithKline

Overview. In January 2011, we entered into a collaboration and license agreement with GSK to discover, develop and commercialize novel small molecule HMT inhibitors directed to available targets from our product platform. Under the terms of the agreement, we granted GSK the option to obtain exclusive worldwide license rights to HMT inhibitors directed to three targets. In March 2014, we and GSK amended certain terms of this agreement for the third target, revising the license terms with respect to candidate compounds and amending the corresponding financial terms, including reallocating milestone payments and increasing royalty rates as to the third target. Additionally, as part of the research collaboration provided for in the agreement, we agreed to provide research and development services related to the licensed targets pursuant to agreed upon research plans during a research term that ended January 8, 2015, or earlier if selection of a development candidate occurred.

Under the agreement, we recorded an upfront payment of $20.0 million and a $3.0 million payment upon the execution of the March 2014 agreement amendment. Through December 31, 2015, we also received $6.0 million of fixed research funding, $15.0 million of preclinical research and development milestone payments and $9.0 million for research and development services. We are eligible to receive up to $18.0 million in additional preclinical research and development milestone payments, up to $109.0 million in clinical development milestone payments, up to $275.0 million in regulatory milestone payments and up to $218.0 million in sales-based milestone payments. In addition, GSK is required to pay us royalties at percentages between the mid-single digits to the low double-digits, on a licensed product-by-licensed product basis, on worldwide net product sales, subject to reductions in specified circumstances.

For each selected target in the collaboration, we were primarily responsible for research until the earlier of selection of a development candidate for the target or January 8, 2015, and GSK is solely responsible for subsequent development and commercialization. GSK provided a fixed amount of research funding during the second and third years of the research term and was obligated to provide research funding equal to 100.0% of mutually agreed research and development costs, subject to specified limitations, for any research activities we conducted in the fourth year of the research term. In December 2013, we and GSK agreed to the selection of a development candidate for one of the three targets under the agreement, after which point GSK became solely responsible for subsequent development and commercialization.

Exclusivity Provisions. Subject to exceptions specified in the agreement, during the term of the agreement, we may not research, develop or commercialize HMT inhibitors directed to the three targets selected by GSK, other than pursuant to the agreement.

Term and Termination. The agreement will expire in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the later of expiration of specified patent coverage or ten years following the first commercial sale. GSK has the right to terminate the agreement at any time with respect to one or more selected targets or in its entirety, upon 90 days prior written notice to us. The agreement may also be terminated with respect to one or more selected targets or in its entirety by either GSK or us in the event of a material breach by the other party. The agreement may be terminated

with respect to selected targets by us in the event GSK participates or actively assists in a legal challenge to one of the patents exclusively licensed to GSK under the agreement with respect to the applicable selected target.

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Eisai

Overview. In March 2015, we entered into an amended and restated collaboration and license agreement with Eisai, under which we reacquired worldwide rights, excluding Japan, to our EZH2 program, including tazemetostat. Under the amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization outside of Japan of tazemetostat and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture tazemetostat and any other EZH2 product candidates in Japan. Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our small molecule HMT inhibitors directed to EZH2, including tazemetostat, while retaining an opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States.

Under the terms of the original agreement, we recorded a $3.0 million upfront payment, $7.0 million in preclinical research and development milestone payments, a $6.0 million clinical development milestone and $22.7 million for research and development services through December 31, 2015. We were also eligible to earn up to a total of $195.0 million in clinical development, regulatory and sales-based milestone payments and to receive royalties on product sales. Upon the execution of the amended and restated collaboration agreement, we agreed to pay Eisai a $40.0 million upfront payment. We also agreed to pay Eisai up to $20.0 million in clinical development milestone payments, up to $50.0 million in regulatory milestone payments and royalties at a percentage in the mid-teens on worldwide net sales of any EZH2 product, excluding net sales in Japan. We are eligible to receive from Eisai royalties at a percentage in the mid-teens on net sales of any EZH2 product in Japan.

Under the original agreement, Eisai was solely responsible for funding all research, development and commercialization costs for licensed compounds. Under the amended agreement, we are solely responsible for funding global development, manufacturing and commercialization costs for EZH2 compounds outside of Japan, and Eisai is solely responsible for funding Japan-specific development and commercialization costs for EZH2 compounds. In connection with the amendment and restatement of our collaboration and license agreement with Eisai, we and Eisai agreed to the transition to us of ongoing development and manufacturing activities that were being conducted by or on behalf of Eisai.

In the event that we seek to license rights to a third party to develop or commercialize an EZH2 product in any country in Asia other than Japan, Eisai has a limited right of first negotiation for such rights. In the event that we are awarded a priority review voucher from the FDA with respect to an EZH2 product, Eisai is entitled to specified compensation if we use the voucher on a non-EZH2 program or sell the voucher to a third party.

Governance. Under the amended and restated collaboration and license agreement, development will be guided by a joint steering committee, with Epizyme retaining final decision making authority with respect to global development.

Exclusivity Restrictions. Subject to exceptions specified in the agreement, for an exclusivity period extending until eight years after the first commercial sale of a product covered by the agreement, neither we nor Eisai may research, develop or commercialize HMT inhibitors directed to EZH2, other than pursuant to the agreement.

Term and Termination. Our agreement with Eisai will remain in effect until the expiration of all payment obligations under the agreement with respect to all licensed products. The royalty term for each licensed product in each country commences on the first commercial sale of the applicable licensed product in the applicable country and ends on the latest of expiration of specified patent coverage, expiration of specified regulatory exclusivity or ten years following the first commercial sale. We or Eisai may terminate the agreement for convenience as to our respective territories, upon 90 days prior written notice. The agreement will also terminate as to our territory if we cease all development

and commercialization activities for the United States and specified major countries in Europe and as to Eisai s territory if Eisai ceases all development and commercialization activities for Japan. The agreement may also be terminated by either party in the event of an

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uncured material breach by the other party or by us in the event Eisai, or an affiliate or sublicensee, participates or actively assists in an action or proceeding challenging or denying the validity of one of our patents. If we terminate the agreement for our convenience, the agreement terminates as a result of our cessation of development and commercialization activities or Eisai terminates the agreement for our uncured material breach, Eisai may elect to have worldwide development and commercialization rights revert to Eisai, and if Eisai so elects, Eisai will be required to pay us specified royalties on net sales of the licensed products and reimburse certain development expenses incurred by us. If Eisai terminates the agreement for its convenience, the agreement terminates as a result of Eisai s cessation of development and commercialization activities or we terminate the agreement for Eisai s uncured material breach or Eisai s, or its affiliate s or sublicensee s, participation in, or assistance with, an action or proceeding challenging or denying the validity of one of our patents, Japanese development and commercialization rights to the licensed products revert to us, and we will be required to pay Eisai specified royalties on net sales of licensed products in Japan.

Companion Diagnostics

Roche. In December 2012, Eisai and we entered into an agreement with Roche under which Eisai and we engaged Roche to develop a companion diagnostic to identify patients who possess certain point mutations of EZH2. In October 2013, this agreement was amended to include additional point mutations in EZH2. The $21.5 million of development costs due under the amended agreement with Roche were the responsibility of Eisai until the execution of our amended and restated collaboration and license agreement with Eisai in March 2015, at which time we assumed responsibility for the remaining development costs due under the agreement. In December of 2015, we entered into the second amendment to the companion diagnostic agreement with Roche. We are responsible for the remaining development costs of $15.0 million due under the second amendment as of December 31, 2015.

Under our agreement with Roche, Roche is obligated to use commercially reasonable efforts to develop and to make commercially available the companion diagnostic. Roche has exclusive rights to commercialize the companion diagnostic.

Our agreement with Roche will expire when we are no longer developing or commercializing tazemetostat. We may terminate the agreement by giving Roche 90 days written notice if we discontinue development and commercialization of tazemetostat or determine, in conjunction with Roche, that the companion diagnostic is not needed for use with tazemetostat. Either we or Roche may also terminate the agreement in the event of a material breach by the other party, in the event of material changes in circumstances that are contrary to key assumptions specified in the agreement or in the event of specified bankruptcy or similar circumstances. Under specified termination circumstances, Roche may become entitled to specified termination fees.

Intellectual Property

We strive to protect the proprietary compounds and technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technologies, diagnostics and other inventions. Our patent portfolio is currently comprised of over 50 issued patents and allowed patent applications and over 400 pending patent applications in the major pharmaceutical markets, that we own as well as license from other parties. In addition to patent protection, we also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents,

maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of HMTs.

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We plan to continue to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment and additional HMT inhibitor compounds and their derivatives. Specifically, we seek patent protection in the United States and internationally for novel compositions of matter covering the compounds, the chemistries and processes for manufacturing these compounds and the use of these compounds in a variety of therapies.

The patent portfolios for our most advanced programs are summarized below.

EZH2. Our EZH2 patent portfolio includes U.S. Patent No. 8,410,088 covering the composition of matter of tazemetostat. This patent issued on April 2, 2013 and is expected to expire in 2032. Our EZH2 portfolio also includes twelve additional U.S. patents and three foreign patents, expected to expire between 2031 and 2034, not including extensions. The claims of these patents cover the composition of matter of EZH2 inhibitor compounds and various methods of their making and use. Patent applications in the same families as these patents are pending in a variety of worldwide jurisdictions, including the United States. The EZH2 program portfolio encompasses more than 30 patent families with pending patent applications relating to compositions of matter and methods of making and use. The patent families in this portfolio are in various stages of prosecution and include patent applications filed in a variety of worldwide jurisdictions, including the United States; Patent Cooperation Treaty (PCT) applications that are eligible for filing in most worldwide jurisdictions, including the United States; and U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. Our patent applications in the EZH2 portfolio, if issued, would be expected to expire between 2031 and 2036.

DOT1L. Our DOT1L patent portfolio includes U.S. Patent No. 8,580,762 covering the composition of matter of pinometostat. The patent issued on November 12, 2013 and is expected to expire in 2032. Our DOT1L portfolio also includes five additional U.S. patents and eight foreign patents, expected to expire between 2031 and 2034, not including extensions. The DOT1L program portfolio encompasses more than seventeen patent families relating to compositions of matter of DOT1L inhibitor compounds and methods of their making and use. The patent families in this portfolio are in various stages of prosecution and include patent families with applications filed in a variety of worldwide jurisdictions including the United States; PCT applications that are eligible for filing in most worldwide jurisdictions, including the United States. These patents and patent applications are wholly owned by us. Our patent applications in the DOT1L portfolio, if issued, would be expected to expire between 2031 and 2036.

Other Targets. We also have patent portfolios directed to targets other than EZH2 and DOT1L, including the HMT targets PRMT1, PRMT3, CARM1 (PRMT4), PRMT5, PRMT6 and PRMT8. Our patent portfolio has more than 20 patent families directed to various product candidates with applications filed in the United States, PCT applications that are eligible for filing in most worldwide jurisdictions, including the United States, and U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. Patents issued in these portfolios are expected to expire between 2033 and 2035. In 2015, the U.S. Patent and Trademark Office issued three U.S. patents that cover PRMT5 inhibitors and methods of their making and use. These patents are expected to expire in 2033, not including extensions. In addition, in 2015 five U.S. patents issued covering PRMT1 inhibitors and methods of their making and use. These patents are expected to expire in 2034, not including extensions.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA

regulatory review process. 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 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

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provisions are available in Europe and other non-United States 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. We intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

UNC In-Licensed Portfolio. In January 2008, we entered into a license agreement with the University of North Carolina at Chapel Hill, or UNC, to discover, develop and commercialize products utilizing specified inventions of UNC. Under the terms of the agreement, we were granted an exclusive, worldwide license under specified patent rights and a non-exclusive worldwide license under specified know-how and biological materials, in each case to discover, develop, manufacture and commercialize pharmaceutical and diagnostic products. The intellectual property we had licensed from UNC did not directly relate to our current product candidates, tazemetostat and pinometostat, and related solely to screening methods and related materials. In March 2016, we terminated this agreement in accordance with its provisions.

Manufacturing

We do not have any manufacturing facilities and currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. Prior to the execution of the amended and restated collaboration and license agreement with Eisai, Eisai manufactured tazemetostat for preclinical and clinical development. Upon execution of the amended and restated collaboration and license agreement, as part of the transition plan, Eisai agreed to sell us its existing inventories and manufacture additional tazemetostat clinical supplies and the active pharmaceutical ingredient, or API. We took receipt of these API and clinical supplies from Eisai during the year ended December 31, 2015. We have entered into clinical supply agreements with two contract manufacturers, one to produce tazemetostat API and one to produce tazemetostat tablets. We intend to identify and qualify additional manufacturers to provide API, tablets and a pediatric formulation as part of our ongoing manufacturing efforts for tazemetostat. To date, we have obtained materials for pinometostat from multiple third party manufacturers.

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

We generally expect to rely on third parties for the manufacture of any companion diagnostics. We are currently collaborating with Roche for a diagnostic for use with tazemetostat, and we expect to rely on Roche for the manufacture of the diagnostic it is developing. We may enter into similar agreements for the manufacture of other companion diagnostics.

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Commercialization

We have not yet established a sales, marketing or product distribution infrastructure because our lead candidates are still in early clinical development. We generally expect to retain commercial rights in the United States for our product candidates for which we receive marketing approvals and have done so to date other than for the product candidates under our GSK collaboration and two of the three targets under our Celgene collaboration. We believe that it will be possible for us to access the United States oncology market through a focused, specialized sales force.

Subject to receiving marketing approvals, we expect to commence commercialization activities by building a focused sales and marketing organization in the United States to sell our products. We believe that such an organization will be able to address the community of oncologists who are the key specialists in treating the patient populations for which our product candidates are being developed. Outside the United States, we may choose to enter into distribution and other marketing arrangements with third parties for any of our product candidates that obtain marketing approval, or may choose to commercialize our products in certain markets, depending upon many factors, including the target market size, availability of reimbursement, and our financial resources at the time.

We also plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with thought leaders in relevant fields of medicine.

We expect that our collaborators for any companion diagnostics we may develop in the future for use with our therapeutic products will hold the commercial rights to these diagnostic products, as is the case for our collaboration with Roche. We expect to coordinate closely with any diagnostic collaborators in connection with the marketing and sale of any related therapeutic products.

Competition

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

There are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. Companies that are developing new epigenetic treatments for cancer that target HMTs include GSK, Novartis AG, Pfizer, Inc., Merck & Co., Inc., Daiichi Sankyo Company Limited and Constellation Pharmaceuticals. In addition, many companies are developing cancer therapeutics that work by targeting epigenetic mechanisms other than HMTs, and some including Celgene and Eisai, are now marketing cancer treatments that work by targeting epigenetic mechanisms other than HMTs.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be

significant competitors, particularly through collaborative arrangements with large and

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established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our therapeutic product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payors seeking to encourage the use of generic products. Generic products that broadly address these indications are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third party payors.

In addition to currently marketed therapies, there are also a number of products in late stage clinical development to treat cancer. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

If our lead product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below.

Tazemetostat. The most common treatments for DLBCL and FL are chemotherapies, usually combined with the monoclonal antibody Rituxan. While Rituxan and number of other widely used anti-cancer agents are labeled either broadly for NHL or more narrowly for DLBCL or FL, no therapies are approved specifically for the treatment of tumors associated with the oncogenic mutation of EZH2. Although there are no approved therapies for MRT, current treatment for these tumors consists of intensive chemotherapy with or without radiation therapy. A doxorubicin-based chemotherapy regimen is used as front line treatment for patients with synovial sarcoma. MRTO is an aggressive tumor with a poor prognosis that is generally treated with surgery and platinum-based combination chemotherapy at diagnosis. Mesothelioma is typically treated with cisplatin and pemetrexed chemotherapy in the front line setting. There are no established salvage treatments for patients with MRT, synovial sarcoma, MRTO, or mesothelioma who relapse or who are refractory to front line treatment.

Pinometostat. There are no approved therapies specifically indicated for MLL-r. There are, however, currently approved therapies for acute lymphoblastic leukemias, or ALL and acute myeloblastic leukemias, or AML, in general. The current standard of care differs according to the specific lineage of the leukemia. Patients with AML and ALL typically are treated with intensive multi-agent chemotherapy and high risk patients who enter remission and have a matched donor may receive an allogeneic stem cell transplant.

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Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and foreign jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA s refusal to approve pending new drug applications, or NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA s good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of human clinical trials, including adequate and well-controlled clinical trials, in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the

facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine GCP compliance;

payment of user fees per published PDUFA guidelines for that year;

FDA review and approval of the NDA; and

compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

Preclinical Studies. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even

after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials. Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on the ClinicalTrials.gov website.

Human clinical trials are typically conducted in four sequential phases, which may overlap or be combined. In phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product. In phase 4, post-approval studies may be conducted to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, phase 2, phase 3 and phase 4 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients.

In general, the FDA accepts foreign safety and efficacy studies that were not conducted under an IND provided that they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. The conduct of these studies must meet at least minimum standards for assuring human subject protection. Therefore, for studies submitted in support of an NDA that were conducted outside the United States and not under an IND, the agency requires demonstration that such studies were conducted in accordance with Good Clinical Practices.

Marketing Approval. Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application

user fee. The application user fee currently exceeds $2.3 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $114,000 per product and $585,000 per establishment for fiscal year 2016. Under the Prescription Drug User Fee

Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data that are adequate 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 product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product s continued safety, quality and purity.

The FDA typically refers a question regarding a novel drug to an external advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA s satisfaction, the FDA will typically issue an approval letter. An approval

letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning,

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

Special FDA Expedited Review and Approval 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 drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. 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 it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. For fast track products, sponsors may have greater interactions with the FDA regarding drug development and may submit sections of a fast track product s NDA before the application is complete.

The FDA may give a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six and ten month review periods are measured from the filing date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive 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 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, the FDA may 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 endpoint, and the drug may be subject to accelerated withdrawal procedures.

Moreover, under the provisions of the new 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 also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

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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.

FDA Regulation of Companion Diagnostics. Our drug products may rely upon *in vitro* companion diagnostics for use in selecting the patients that we believe will respond to our cancer therapeutics. FDA officials have issued guidance that addresses issues critical to developing *in vitro* companion diagnostics, such as when the FDA will require that the diagnostic and the drug be approved simultaneously. The guidance issued in August 2014 states that if safe and effective use of a therapeutic product depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of the diagnostic at the same time that the FDA approves the therapeutic product.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the cancer treatment to obtain Pre-Market Approval, or PMA, simultaneously with approval of the drug. Based on the guidance, and the FDA s past treatment of companion diagnostics, we believe that the FDA will require PMA approval of one or more *in vitro* companion diagnostics to identify patient populations suitable for our cancer therapies. The review of these *in vitro* companion diagnostics in conjunction with the review of our cancer treatments involves coordination of review by the FDA s Center for Drug Evaluation and Research and by the FDA s Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device s safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds $250,000 for most PMAs.

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

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, 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.

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may

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result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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

Federal and State Fraud and Abuse and Data Privacy and Security Laws and Regulations. In addition to FDA restrictions on marketing of pharmaceutical products, federal and state fraud and abuse laws restrict business practices in the biopharmaceutical industry. These laws include anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations.

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 or recommending the purchase, lease, or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been broadly interpreted to include anything of value. The Anti-Kickback 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 common activities from prosecution, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing,

purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

The reach of the Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively PPACA, which, among other things, amended the intent requirement of the federal Anti-Kickback Statute such that 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, PPACA 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

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for purposes of the civil False Claims Act 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. PPACA also created new federal requirements for reporting, by applicable manufacturers of covered drugs, payments and other transfers of value to physicians and teaching hospitals.

The federal 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. A claim includes any request or demand for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted 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 prosecuted for causing false claims to be submitted because of the companies marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit 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. 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.

We may also 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 the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, imposes specified 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, defined as 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 certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In addition, federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, require certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures

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.

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Coverage and Reimbursement. The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental authorities, private health insurers and other third party payors provide coverage for and establish adequate reimbursement levels for our therapeutic product candidates and related companion diagnostics. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third party payors often provide reimbursement for products and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. 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 often has resulted in average selling prices lower than they would otherwise be. Further, 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 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.

Third party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for our product candidates in whole or in part.

Impact of Healthcare Reform on Coverage, Reimbursement, and Pricing. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for

Health, and periodic reports on the status of the research and related expenditures will be made to

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Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives, including, most recently, PPACA, which became law in March 2010 and substantially changes the way healthcare is financed by both governmental and private insurers. Among the provisions of the Affordable Care Act of importance to potential drug candidates are:

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

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

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

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

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

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

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

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

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

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Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Exclusivity and Approval of Competing Products

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

Hatch-Waxman Patent Exclusivity. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant s product or a 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 competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) NDA.

Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths, dosage form and route of administration as the listed drug and has been shown to be bioequivalent through *in vitro* or *in vivo* testing or otherwise to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. 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.

A 505(b)(2) application applies to a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. As with an ANDA, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. 505(b)(2) NDAs generally are submitted for changes to a previously approved drug product, such as a new dosage form or indication.

The ANDA or 505(b)(2) NDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA s Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

the required patent information has not been filed;

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the listed patent has expired;

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

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

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except when the ANDA or 505(b)(2) NDA applicant challenges a listed drug. A certification that the proposed product will not infringe the already approved product s listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA or 505(b)(2) NDA 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 application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of notice of the Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA 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 applicant.

Hatch Waxman Non-Patent Exclusivity. Market and data exclusivity provisions under the FDCA also can delay the submission or the approval of ANDAs and 505(b)(2) NDAs for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Orphan Drug Exclusivity. The Orphan Drug Act provides incentives for the development of drugs intended to treat rare diseases or conditions, which generally are diseases or conditions affecting less than 200,000 individuals annually in the United States. If a sponsor demonstrates that a drug is intended to treat a rare disease or condition, the FDA grants orphan drug designation to the product for that use. The benefits of orphan drug designation include research and development tax credits and exemption from user fees. A drug that is approved for the orphan drug designated

indication is granted seven years of orphan drug exclusivity. During that period, the FDA generally may not approve any other application for the same product for the same indication, although there are exceptions, most notably when the later product is shown to be clinically superior to the product with exclusivity. We intend to seek orphan drug designation and exclusivity for our products whenever it is available.

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We have been granted orphan drug designation in the United States and the European Union for pinometostat, and orphan drug designation in the United States for tazemetostat for the treatment of malignant rhabdoid tumors.

Pediatric Exclusivity. Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan drug exclusivity periods described above. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA s request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve an ANDA or 505(b)(2) application owing to regulatory exclusivity or listed patents. When any of our products is approved, we anticipate seeking pediatric exclusivity when it is appropriate.

European Union Drug Approval Process

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Clinical Trial Approval in the EU. Pursuant to the currently applicable Clinical Trials Directives, an applicant must obtain approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. In April 2014, the EU adopted a new Clinical Trials Regulation, which is set to replace the current Clinical Trials Directive. The new Clinical Trials Regulation will be directly applicable to and binding in all 28 EU Member States without the need for any national implementing legislation, and will become applicable no earlier than 28 May 2016. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State (RMS) through an EU Portal. The submission procedure will be the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

Marketing Authorization. To obtain marketing approval of a drug under European Union regulatory systems, we may submit marketing authorization applications, or MAAs, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all European Union member states. The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of specified diseases, and optional for those products that are highly innovative or for which a centralized process is in the interest of patients. Under the centralized procedure in the European Union, the maximum

timeframe for the evaluation of an MAA is 210 days, excluding clock stops,

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when additional written or oral information is to be provided by the applicant in response to questions asked by the Scientific Advice Working Party of the Committee of Medicinal Products for Human Use, or the CHMP. Accelerated evaluation 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, such as 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, the European Medicines Agency, or EMA, ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state, known as the reference member state. Under this procedure, an applicant submits an application, or dossier, and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state s assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points may eventually be referred to the European Commission, whose decision is binding on all member states. For the EMA, a Pediatric Investigation Plan, or a request for waiver or deferral, is required for submission prior to submitting an MAA for use for drugs in pediatric populations.

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

Orphan Drug Exclusivity. The EMA grants orphan drug designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union. In addition, orphan drug designation can be granted if the drug is intended for a life threatening, seriously debilitating or serious and chronic condition in the European Union and without incentives it is unlikely that sales of the drug in the European Union would be sufficient to justify developing the drug. Orphan drug designation is only available if there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation provides opportunities for free protocol assistance, fee reductions for access to the centralized regulatory procedures before and during the first year after marketing authorization and 10 years of market exclusivity following drug approval. Fee reductions are not limited to the first year after authorization for small and medium enterprises. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Employees

As of March 1, 2016, we had 89 full-time employees, 61 of whom were primarily engaged in research and development activities and 27 of whom have an M.D. or Ph.D. degree.

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Executive Officers of the Company

The following table sets forth the name, age and position of each of our executive officers as of March 1, 2016.

Name	Age	Position
Robert B. Bazemore	48	President, Chief Executive Officer and Director
Andrew E. Singer	45	Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer
Robert A. Copeland, Ph.D.	59	President of Research and Chief Scientific Officer
Peter T.C. Ho, M.D., Ph.D.	54	Chief Development Officer

Robert B. Bazemore has served as a director and our President and Chief Executive Officer since joining us in September 2015. Prior to joining us, from September 2014 to July 2015, Mr. Bazemore, served as the Chief Operating Officer of Synageva BioPharma Corp., a biopharmaceutical company developing therapeutic products for rare disorders. Prior to joining Synageva, Mr. Bazemore served in increasing levels of responsibility at Johnson & Johnson, a healthcare company, including Vice President, Centocor Ortho Biotech Sales & Marketing from 2008 to 2010, President of Janssen Biotech from March 2010 to October 2013 and Vice President of Global Surgery at Ethicon from October 2013 to September 2014. Prior to Johnson & Johnson, Mr. Bazemore worked at Merck & Co., Inc. for eleven years, where he served in a variety of roles in medical affairs, sales and marketing. Mr. Bazemore is the chairman of the board of Pennsylvania Bio, a life sciences industry group. He received a B.S. in biochemistry from the University of Georgia.

Andrew E. Singer has served as our Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer since February 2015. Prior to joining us, from 2004 to January 2015, Mr. Singer served in increasing levels of responsibility in the Health Care Investment Banking Group at RBC Capital Markets Corporation, or RBC, an investment bank, serving as a Managing Director from 2007 to 2015. Prior to joining RBC, Mr. Singer worked at Petkevitch & Company, co-founded MVC Capital, and worked at Robertson, Stephens & Co, The Shansby Group and The Blackstone Group. Mr. Singer serves on the board of directors of the J.F. Kapnek Trust. Mr. Singer received a B.A. from Yale University and an M.B.A. from Harvard University Graduate School of Business.

Robert A. Copeland, Ph.D. has served as our President of Research and Chief Scientific Officer since January 2015 and previously served as our Executive Vice President and Chief Scientific Officer from September 2008 to January 2015. Prior to joining us, from January 2003 to September 2008, Dr. Copeland was Vice President, Cancer Biology, Oncology Center of Excellence in Drug Discovery, at GSK, a pharmaceutical company. Before joining GSK, Dr. Copeland held scientific staff positions at Merck Research Laboratories of Merck and Bristol-Myers Squibb Company, a biopharmaceutical company, and a faculty position at the University of Chicago Pritzker School of Medicine. Dr. Copeland received a B.S. in chemistry from Seton Hall University, a Ph.D. in chemistry from Princeton University and did postdoctoral studies as the Chaim Weizmann Fellow at the California Institute of Technology.

Peter T.C. Ho, M.D., Ph.D. has served as our Chief Development Officer since September 2014. Prior to joining us, from February 2013 to September 2014, Dr. Ho served as Chief Executive Officer of Metastagen Inc., a pharmaceutical preparation company that he co-founded. Prior to that, Dr. Ho served as President of BeiGene Ltd., a biopharmaceutical company that he co-founded, from October 2010 to December 2012, as Vice President of Oncology Development at Johnson & Johnson from September 2008 to September 2010 and, prior to that, as Senior Vice President of the Oncology Center of Excellence for Drug Development at GSK. Dr. Ho is a board-certified pediatric hematologist/oncologist and was formerly a fellow at the Dana-Farber Cancer Institute, the National Cancer Center Institute, or NCI, and the FDA. He received a B.A. in biology from the Johns Hopkins University and an M.D.

and Ph.D. (pharmacology) from the Yale University School of Medicine.

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Our Corporate Information

We were incorporated under the laws of the state of Delaware on November 1, 2007 under the name Epizyme, Inc. Our principal executive offices are located at 400 Technology Square, Cambridge, Massachusetts 02139. Our telephone number is (617) 229-5872, and our website is located at www.epizyme.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, are available free of charge on our website located at www.epizyme.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (the SEC). These reports are also available at the SEC s Internet website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC s Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.epizyme.com, under Investor Center and are available in print to any person who requests copies by contacting Epizyme by calling (617) 229-5872 or by writing to Epizyme, Inc., 400 Technology Square, Cambridge, Massachusetts 02139.

Item 1A. Risk Factors

Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC, in evaluating the Company and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

Risks Related to the Discovery and Development of Our Product Candidates

Our research and development is focused on the creation of novel epigenetic therapies for cancer patients, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs is novel and may never lead to marketable products.

The discovery of novel epigenetic therapies for cancer patients is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. Although epigenetic regulation of gene expression plays an essential role in biological function, few drugs premised on epigenetics have been discovered. Moreover, those drugs based on an epigenetic mechanism that have received marketing approval are in different target classes than HMTs, where our research and development is principally focused. Although preclinical studies suggest that genetic alterations can result in changes to the activity of HMTs, making them oncogenic, to date no company has translated these biological observations into systematic drug

discovery that has yielded a drug that has received marketing approval. We believe that we are the first company to conduct a clinical trial of an HMT inhibitor. Therefore, we do not know if our approach of inhibiting HMTs to treat cancer patients will be successful.

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We are early in our development efforts and have only two product candidates in clinical trials. All of our other product candidates are still in preclinical development. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts and have only two product candidates in clinical trials. All of our other product candidates are still in preclinical development. We have invested substantially all our efforts and financial resources in the identification and preclinical and clinical development of inhibitors of HMTs and other CMPs. Our ability to generate product revenues, which we do not expect will occur for several years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- making arrangements with third party manufacturers for, or establishing, commercial manufacturing capabilities;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of the products, if and when approved, by patients, the medical community and third party payors;
- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- protecting our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of the products following approval.

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

We may not be successful in our efforts to use and expand our proprietary drug discovery platform to build a pipeline of product candidates.

A key element of our strategy is to use and expand our proprietary drug discovery platform to build a pipeline of small molecule inhibitors of HMT and other CMP targets and progress these product candidates through clinical development for the treatment of a variety of different types of cancer. Although our research and development efforts to date have resulted in a pipeline of programs directed to specific HMT and other CMP targets, we may not be able to develop product candidates that are safe and effective CMP inhibitors. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our technological approach, we will not be able to obtain product revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

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Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Two of our product candidates are in clinical development, and our remaining product candidates are in preclinical development. The risk of failure for each of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans.

Product candidates are subject to continued preclinical safety studies, which may be conducted concurrent with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical studies. For example, in the course of our preclinical safety studies of tazemetostat, we observed the development of lymphoma in Sprague Dawley rats. We informed the relevant international regulatory authorities, the FDA and the clinical investigators of this finding in rats, and discussed the results with the regulatory authorities. In August 2015, the FDA accepted our IND for tazemetostat in patients with INI1-negative tumors or synovial sarcoma, and in December 2015, the FDA accepted our IND for tazemetostat in patients with DLBCL. Expansion of our development of tazemetostat outside of these indications in the United States, including mesothelioma characterized by BAP1 loss-of-function, will require that we submit an IND or that we submit supplemental materials to the FDA and that we address this matter to the satisfaction of the FDA within the context of patient risk-benefit and in view of the safety and efficacy data from our ongoing and completed clinical trials of tazemetostat. If we are unable to adequately address this matter, we may be unable to conduct clinical trials of tazemetostat in patients with other cancers in the United States, our trials may be limited to certain patient populations or our ability to conduct other trials in the United States may be delayed.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, the complete responses that were observed in two patients with MLL-r in the fourth dose cohort of the dose escalation portion of our phase 1 clinical trial of pinometostat were not achieved by any other patient treated with pinometostat in the phase 1 clinical trial. We voluntarily ceased patient enrollment into the phase 1 clinical trial in adult patients with MLL-r due to insufficient evidence of efficacy of pinometostat as a monotherapy in the third quarter of 2015. We are continuing to conduct a phase 1 dose escalation trial of pinometostat in pediatric patients with MLL-r. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

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

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

we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trials or abandon product development programs;

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

- our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;

- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

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

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

- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

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

- be delayed in obtaining marketing approval for our product candidates;

- not obtain marketing approval at all;

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

- obtain approval with labeling or a risk evaluation mitigation strategy that includes significant use or distribution restrictions or safety warnings;

- be subject to additional post-marketing testing requirements; or

have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in clinical testing or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. In particular, because certain of our products may be focused on specific patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for product candidates that may treat the broader patient populations within which our product candidates are being developed for the treatment of a subset of identifiable cancer patients, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors product candidates. For

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instance, our ongoing clinical trials of tazemetostat in adult and pediatric patients with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma are targeting rare patient populations. As such, these trials may be slow to enroll. In addition, our phase 2 clinical trial of tazemetostat in patients with NHL has two arms targeting patients with EZH2 mutations in their tumors, one in germinal center B-cell, or GCB, DLBCL and one in follicular lymphoma. We believe that patients with these mutations represent only between 15% and 25% of the total GCB DLBCL and follicular lymphoma population in the United States and other major reimbursable markets. As such, these arms of the NHL phase 2 study have been, and are likely to continue to be, slower to enroll than the other three arms of the phase 2 NHL clinical trial.

Patient enrollment is affected by other factors including:

- the severity of the disease under investigation;
- the eligibility criteria for the trial in question;
- the perceived risks and benefits of the product candidate under trial;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

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

If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

If our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected in clinical trials or preclinical testing, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In pharmaceutical development, many compounds that initially show promise in early stage testing for treating cancer are later found to cause side effects that prevent further development of the compound.

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

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

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If we are unable to successfully develop companion diagnostics for our therapeutic product candidates when needed, or experience significant delays in doing so, we may not achieve marketing approval or realize the full commercial potential of our therapeutic product candidates.

We may develop companion diagnostics for our therapeutic product candidates to identify patients for our clinical trials who have the specific cancers that we are seeking to treat as appropriate and when existing, available technology may not be sufficient to identify those patients. We do not have experience or capabilities in developing or commercializing diagnostics and plan to rely in large part on third parties to perform these functions. For example, we have entered into an agreement with Roche to develop and commercialize a companion diagnostic for use with tazemetostat for NHL patients with EZH2 point mutations. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside of the United States as medical devices and require separate regulatory approval prior to commercialization. If any third parties that we engage to assist us, are unable to successfully develop companion diagnostics that are needed for our therapeutic product candidates, or experience delays in doing so:

- the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our therapeutic product candidates may not receive marketing approval if their safe and effective use depends on a companion diagnostic; and
- we may not realize the full commercial potential of any therapeutic product candidates that receive marketing approval if, among other reasons, we are unable to appropriately identify patients with the specific genetic alterations targeted by our therapeutic product candidates.

If any of these events were to occur, our business would be harmed, possibly materially.

Risks Related to Our Financial Position and Need For Additional Capital

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $132.4 million for the year ended December 31, 2015. As of December 31, 2015, we had an accumulated deficit of $243.5 million. To date, we have financed our operations primarily through our collaborations, our public offerings, and private placements of our preferred stock. All of our revenue to date has been collaboration revenue. We have devoted substantially all of our financial resources and efforts to research and development, including clinical and preclinical studies. We are still in the early to middle stages of development of our product candidates, and we have not completed development of any drug candidates. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will continue to increase over the next several years as we:

- continue our phase 2 clinical trial of tazemetostat for the treatment of patients with NHL, our phase 2 clinical trial of tazemetostat for the treatment of adult patients with certain genetically-defined solid tumors and our

phase 1 clinical trial of tazemetostat for the treatment of pediatric patients with certain genetically-defined solid tumors;

initiate our planned clinical trials of tazemetostat in combination with R-CHOP in front line elderly patients with DLBCL and in combination with either an anti-PD1 antibody or an anti-PDL1 antibody in patients with relapsed or refractory DLBCL;

initiate our planned phase 2 clinical trial of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function;

continue our phase 1 clinical trial of tazemetostat for the treatment of patients with relapsed or refractory NHL or advanced solid tumors and our phase 1 clinical trial of pinometostat in pediatric patients with MLL-r;

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pay any milestone payments provided for and achieved under the amended and restated collaboration and license agreement with Eisai;

conduct research and development for Celgene under our amended and restated collaboration and license agreement;

continue the research and development of our other product candidates;

seek to discover and develop additional product candidates;

seek regulatory approvals for any product candidates that successfully complete clinical trials;

ultimately establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval;

maintain, expand and protect our intellectual property portfolio;

hire additional clinical, quality control and scientific personnel; and

add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

We expect our use of cash to significantly increase as a result of the amended and restated collaboration and license agreement with Eisai. Upon the execution of the amended and restated collaboration and license agreement, we paid Eisai a $40.0 million upfront payment. We also agreed to pay Eisai up to $20.0 million in clinical development milestone payments, up to $50.0 million in regulatory milestone payments and royalties at a percentage in the mid-teens on worldwide net sales of any EZH2 product, excluding net sales in Japan. In addition, we are responsible for solely funding global development, manufacturing and commercialization costs for EZH2 compounds as well as the remaining development costs of $15.0 million as of December 31, 2015 under the companion diagnostic agreement with Roche. Prior to the amended and restated agreement, Eisai was responsible for solely funding all research, development and commercialization costs for licensed compounds.

To become and remain profitable, we must succeed in developing, and eventually commercializing, a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of

increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA, the European Medicines Agency, or EMA, or other regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause our stockholders to lose all or part of their investment in our company.

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

We expect our expenses to increase in connection with our ongoing activities, particularly since we have assumed responsibility for the funding of the EZH2 program, including our ongoing phase 2 clinical trial of

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tazemetostat for the treatment of patients with NHL, our ongoing phase 2 clinical trial of tazemetostat for the treatment of adult patients with certain genetically-defined solid tumors and our ongoing phase 1 clinical trial of tazemetostat for the treatment of pediatric patients with certain genetically-defined solid tumors; initiate our planned combination clinical trials of tazemetostat in combination with R-CHOP in front line elderly patients with DLBCL and in combination with either an anti-PD1 antibody or an anti-PDL1 antibody in patients with relapsed or refractory DLBCL; initiate our planned phase 2 study of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function; continue our phase 1 clinical trial of tazemetostat for the treatment of patients with relapsed or refractory NHL or advanced solid tumors and our phase 1 clinical trial of pinometostat in pediatric patients with MLL-r; pay any milestone payments provided for and achieved under the amended and restated collaboration and license agreement with Eisai; continue research for Celgene under our amended and restated collaboration and license agreement; and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these product candidates and other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents as of December 31, 2015 together with the proceeds from our offering of common stock in January 2016, will be sufficient to fund our operating expenses and capital expenditure requirements through at least the end of 2017. We have based these expectations on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Our future capital requirements will depend on many factors, including:

- our remaining collaboration agreements remaining in effect and our ability to obtain global development co-funding and achieve milestones under these agreements;
- the progress and results of our ongoing and planned clinical trials of tazemetostat, and our ongoing phase 1 clinical trial of pinometostat in pediatric patients;
- the number and development requirements of additional indications for tazemetostat, pinometostat and other product candidates that we may pursue, including the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for such product candidates;
- our ongoing research for Celgene under our amended and restated collaboration and license agreement;
- the costs, timing and outcome of regulatory review of our product candidates;
- milestones, option exercise fees, license fees, and other collaboration-based revenues, if any;

the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution for any of our product candidates for which we receive marketing approval;

the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

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

the extent to which we acquire or in-license other products and technologies.

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

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products that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and development agreements with collaboration partners. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing stockholders will be diluted and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Our limited operating history may make it difficult to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in early 2008, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and, beginning in 2012, conducting clinical trials. All but two of our product candidates are still in preclinical development. We are conducting a phase 2 clinical trial of tazemetostat for the treatment of patients with NHL, a phase 2 clinical trial of tazemetostat for the treatment of adult patients with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma, a phase 1 clinical trial of tazemetostat for the treatment of pediatric patients with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma, a phase 1 clinical trial of tazemetostat for the treatment of patients with NHL and solid tumors, and a phase 1 clinical trial of pinometostat in pediatric patients with MLL-r. We have not yet demonstrated our ability to successfully complete any clinical trials, obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history.

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

We expect our financial condition and operating results to continue to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, the results of any quarterly or annual periods should not be relied upon as indications of future operating performance.

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Risks Related to the Commercialization of Our Product Candidates

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

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the availability of third party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products together with other medications.

If we are unable to establish sales, marketing and distribution capabilities, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales and marketing organization.

In the future, we expect to build a focused sales and marketing infrastructure to market some of our product candidates in the United States, and potentially in international markets, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any

reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

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, and will likely 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 many 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.

Specifically, there are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. Companies that are developing new epigenetic treatments for cancer that target HMTs, include GSK, Novartis AG, Pfizer, Inc., Merck & Co., Inc., Daiichi Sankyo Company Limited and Constellation Pharmaceuticals. In addition, many companies are developing cancer therapeutics that work by targeting epigenetic mechanisms other than HMTs, and some including Celgene and Eisai, are now marketing cancer treatments that work by targeting epigenetic mechanisms other than HMTs.

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

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and

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

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third party reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or 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 in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. 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.

Our ability to commercialize any product candidates successfully also 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. Government authorities and third party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the 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. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

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

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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. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will 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;

injury to our reputation and significant negative media attention;

withdrawal of clinical trial participants;

significant costs to defend any related litigation;

substantial monetary awards to trial participants or patients;

loss of revenue;

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

the inability to commercialize any products that we may develop.

We currently hold $10.0 million in product liability insurance coverage in the aggregate, with a per incident limit of $10.0 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. 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.

Risks Related to Our Dependence on Third Parties

Our existing therapeutic collaborations are important to our business, and future collaborations may also be important to us. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

We have limited capabilities for drug development and do not yet have any capability for sales, marketing or distribution. Accordingly, we have entered into therapeutic collaborations with other companies that we believe can provide such capabilities, including our collaboration and license agreements with Celgene and GSK. With our reacquisition of tazemetostat rights under our amended and restated collaboration and license agreement with Eisai,

we no longer have access to such capabilities for tazemetostat except with Eisai in Japan. Our collaborations have provided us with important funding for our development programs and product platform and we expect to receive additional funding under these collaborations in the future. Our existing therapeutic collaborations, and any future collaborations we enter into, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

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

product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;

a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

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

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

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

collaborations may be terminated for the convenience of the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

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

Our existing therapeutic collaborations contain restrictions on our engaging in activities that are the subject of the collaboration with third parties for specified periods of time. For example, under our collaboration agreement with Celgene, subject to specified exceptions, we may not, during the option period, research, develop or commercialize inhibitors directed to DOT1L and the three option targets covered by the agreement outside of the collaboration. These restrictions may have the effect of preventing us from undertaking development and other efforts that may appear to be attractive to us.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

For some of our product candidates or for some HMT targets, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for development and potential commercialization of therapeutic

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products. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator s evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

Failure of our third party collaborators to successfully commercialize companion diagnostics developed for use with our therapeutic product candidates could harm our ability to commercialize these product candidates.

We do not plan to develop companion diagnostics internally and, as a result, we are dependent on the efforts of our third party collaborators to successfully commercialize companion diagnostics when existing, available technology may not be sufficient to identify patients for treatment with our therapeutic product candidates. Our collaborators:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the companion diagnostics;
- may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;
- may not pursue commercialization of any therapeutic product candidates that achieve regulatory approval;
- may elect not to continue or renew commercialization programs based on changes in the collaborators strategic focus or available funding, or external factors such as an acquisition, that divert resources or create competing priorities;
- may not commit sufficient resources to the marketing and distribution of such product or products; and
- may terminate their relationship with us.

If companion diagnostics for use with our therapeutic product candidates fail to gain market acceptance, our ability to derive revenues from sales of our therapeutic product candidates could be harmed. If our collaborators fail to commercialize these companion diagnostics, we may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with our therapeutic product

candidates or do so on commercially reasonable terms, which could adversely affect and delay the development or commercialization of our therapeutic product candidates.

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely on third party clinical research organizations to conduct our ongoing phase 2 clinical trial of tazemetostat for the treatment of patients with NHL, phase 2 clinical trial of tazemetostat for the treatment of adult patients with certain genetically-defined solid tumors, phase 1 clinical trial of tazemetostat for the treatment of pediatric patients with certain genetically-defined solid tumors, phase 1 clinical trial of tazemetostat for the treatment of patients with NHL and solid tumors and phase 1 clinical trial of pinometostat in pediatric patients

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with MLL-r, and plan to rely on third party clinical research organizations to conduct our planned clinical trials of tazemetostat in combination with R-CHOP in front line elderly patients with DLBCL and in combination with an anti-PD1 antibody and an anti-PDL1 antibody in patients with relapsed or refractory DLBCL and our planned phase 2 study of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function. We do not plan to independently conduct clinical trials of our other product candidates. We expect to continue to rely on third parties, such as clinical research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities might be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

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

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

We do not have any manufacturing facilities and rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We also expect to rely on third party manufacturers or third party collaborators for the manufacture of commercial supply of any other product candidates for which our collaborators or we obtain marketing approval.

We may be unable to establish any agreements with third party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third party manufacturers, reliance on third party manufacturers entails additional risks, including:

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

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

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the possible misappropriation of our proprietary information, including our trade secrets and know-how; and

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

Third party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside of the United States. Our failure, or the failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent

law restricts the patentability of methods of treatment of the human body more than

United States law does. 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 at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. 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.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. 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 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 non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our drug candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates. We intend to seek patent term extensions for any of our issued patents in any jurisdiction where they are available, however there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

Recent 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 United States patent law. These changes include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, 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, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, 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, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage.

Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

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The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, 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 of our technology and products. 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. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent s claims narrowly or 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 or interpreted narrowly.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights, that are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we may be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

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

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. 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 U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

If we are found to infringe a third party s intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force

us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are party to license and research agreements that impose, and we may enter into additional licensing and funding arrangements with third parties that may impose, diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Under our existing licensing and funding agreements, we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreements. We also had diligence and development obligations under those agreements that we have satisfied. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee s former employer. Litigation may be necessary to defend against these claims.

In addition, while 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, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, 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 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 litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

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

and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

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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 product candidates, 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, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

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

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside of the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third party CROs to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate s safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. For example, we voluntarily ceased patient enrollment in our phase 1 clinical trial of pinometostat in adult patients with MLL-r due to insufficient evidence of efficacy with monotherapy treatment. New cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a

variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process

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and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

We may not be able to obtain orphan drug exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

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

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

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

A fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.

We intend to seek fast track designation for one or more of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

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A breakthrough therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a breakthrough therapy designation for some of our product candidates. 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. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive breakthrough therapy designation, the receipt of such designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in that jurisdiction.

In order to market and sell our products in the European Union and many other foreign jurisdictions, we or our third party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our third party collaborators may not obtain approvals from regulatory authorities outside of the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. 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 required by the FDA to obtain approval of a companion diagnostic in connection with approval of a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. Under the Federal Food, Drug, and Cosmetic Act, companion

diagnostics are regulated as medical devices, and the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain Premarket Approval, or a PMA, for the diagnostic. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, involves a rigorous premarket review during which the

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applicant must prepare and provide the FDA with reasonable assurance of the device s safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA approval is not guaranteed and may take considerable time, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. As a result, if we are required by the FDA to obtain approval of a companion diagnostic for a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we may not be able to commercialize the product candidate on a timely basis or at all and our ability to generate revenue will be materially impaired.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a risk evaluation and mitigation strategy. New cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ imposes stringent restrictions on manufacturers communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

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

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;

requirements to conduct post-marketing studies or clinical trials;

warning letters or untitled letters;

withdrawal of the products from the market;

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

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recall of products;

fines, restitution or disgorgement of profits or revenues;

suspension or withdrawal of marketing approvals;

damage to relationships with any potential collaborators;

unfavorable press coverage and damage to our reputation;

refusal to permit the import or export of our products;

product seizure;

injunctions or the imposition of civil or criminal penalties; or

litigation involving patients using our products.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union s requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

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

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

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

such as Medicare and Medicaid;

the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim;

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

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

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the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, 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 information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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

Recently enacted and future legislation 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.

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 profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the PPACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the PPACA of importance to our potential product candidates are the following:

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

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

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

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

extension of manufacturers Medicaid rebate liability;

expansion of eligibility criteria for Medicaid programs;

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

requirements to report financial arrangements with physicians and teaching hospitals;

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

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

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 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 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.

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

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

us to more stringent product labeling and post-marketing testing and other requirements.

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

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

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If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm 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 for failure to comply with such laws and regulations.

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

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

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

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

Risks Related to Employee Matters and Managing Growth

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

We are highly dependent on the research and development, clinical and business expertise of our executive officers as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment letter agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain key person insurance for any of our executives or other employees.

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Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies, universities and research institutions for similar personnel. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

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

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

Risks Related to Our Common Stock

Our executive officers and directors and their affiliates, if they choose to act together, may have the ability to significantly influence all matters submitted to stockholders for approval.

As of March 1, 2016, our executive officers and directors and their affiliates beneficially own, in the aggregate, shares representing approximately 32% of our common stock. As a result, if these stockholders were to choose to act together, may be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

delay, defer or prevent a change in control;

entrench our management and board of directors; or

impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

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

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

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

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

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

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

The price of our common stock has been and may in the future be volatile and fluctuate substantially.

Our stock price has been and may in the future be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. From October 1, 2014 until March 1, 2016, the sale price of our common stock as reported on the NASDAQ Global Market ranged from a high of $30.26 to a low of $8.27. The market price for our common stock may be influenced by many factors, including:

the success of competitive products or technologies;

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- results of clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license 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 the financial results of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this Risk Factors section.

We have broad discretion over the use of our cash and cash equivalents and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

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

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company through 2018. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive, as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of these

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accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

As a public company, and particularly after we are no longer an emerging growth company, we will continue to incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and make some activities more time-consuming and costly.

We cannot predict or estimate the amount of additional costs we may incur to continue to operate as a public company, nor can we predict the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we are not required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be the sole source of gain for our stockholders.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

If securities or industry analysts do not continue to publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock may be impacted, in part, by the research and reports that securities or industry analysts publish about us or our business. There can be no assurance that analysts will cover us, continue to

cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price may decline. In addition, if one or more analysts cease coverage of our company or

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fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located in Cambridge, Massachusetts, where we occupy approximately 42,500 square feet of office and laboratory space. The term of the Cambridge lease expires November 30, 2017. In addition, we occupy approximately 4,000 square feet of office space in Durham, North Carolina. The term of the Durham lease expires on July 31, 2017.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

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PART II

Item 5. Market for the Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock is traded on the NASDAQ Global Market under the symbol EPZM. Trading of our common stock commenced on May 31, 2013, following the completion of our initial public offering. The following table sets forth the high and low sale prices per share of our common stock, as reported on the NASDAQ Global Market, for the periods indicated:

	Market Price	
	High	**Low**
Year ended December 31, 2015:		
Fourth quarter	$ 18.29	$ 11.26
Third quarter	$ 25.25	$ 12.00
Second quarter	$ 28.48	$ 15.51
First quarter	$ 25.48	$ 16.63
Year ended December 31, 2014:		
Fourth quarter	$ 30.26	$ 16.51
Third quarter	$ 40.98	$ 25.10
Second quarter	$ 31.35	$ 18.75
First quarter	$ 41.23	$ 19.76

As of March 1, 2016, the number of holders of record of our common stock was 21. This number does not include beneficial owners whose shares are held in street name.

Dividends

We have never declared or paid cash dividends on our capital stock. We intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends to our stockholders in the foreseeable future.

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Stock Performance Graph

The following graph shows a comparison from May 31, 2013, the first date that shares of our common stock were publicly traded, through December 31, 2015 of the cumulative total return on an assumed investment of $100.00 in cash in our common stock, the NASDAQ Composite Index and the NASDAQ Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance. Data for the NASDAQ Composite Index and NASDAQ Biotechnology Index assume reinvestment of dividends.

The performance graph in this Item 5 is not deemed to be soliciting material or to be filed with the SEC for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any of our filings under the Securities Act of 1933 or the Securities Exchange Act of 1934, except to the extent we specifically incorporate it by reference into such a filing.

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Item 6. Selected Financial Data

The following selected financial data has been derived from our consolidated financial statements. The information set forth below should be read in conjunction with Item 7. *Management s Discussion and Analysis of Financial Condition and Results of Operations* and with our consolidated financial statements and notes thereto included elsewhere in this document.

	Year Ended December 31,				
	2015	2014	2013	2012	2011
	(In thousands, except per share data)				
Consolidated Statements of Operations Data:					
Collaboration revenue	$ 2,560	$ 41,411	$ 68,482	$ 45,222	$ 6,944
Operating expenses:					
Research and development	111,209	75,595	57,567	38,482	22,911
General and administrative	23,900	20,866	14,042	7,508	5,000
Total operating expenses	135,109	96,461	71,609	45,990	27,911
Operating loss	(132,549)	(55,050)	(3,127)	(768)	(20,967)
Other income (expense), net	173	154	(7)	67	10
Income tax expense		109	349	1	

(Dollars in Thousands)
(Unaudited)

	Six months ended January 31	
	2013	2012
Operating activities:		
Net income	$ 117	$ 333
Adjustments to reconcile net income to net cash provided by operating activities:		
Amortization of software products	860	685
Amortization of discount related to present value	(16)	(23)

of earnout		
Amortization of bank loan fees	165	-
Depreciation and other amortization	619	807
Provision for bad debt allowance	50	15
Deferred income taxes	(766)	205
Stock based compensation related to stock options	85	43
Stock issued as contribution to 401(k) plan	-	55
Net change in assets and liabilities:		
Trade receivables	(83)	116
Work in process	(57)	3
Prepaid expenses and other	260	35
Other long term assets	(140)	9
Accounts payable	681	(186)
Deferred revenue	(710)	(427)
Accrued payroll and related liabilities	280	(286)
Accrued sales, use and income taxes	(92)	(30)
Other accrued liabilities	124	21
Net cash provided by operating activities	$ 1,377	$ 1,375
Investing activities:		
	(435)	(211)

Purchase of equipment, software and leasehold improvements		
Cash received from disposition of a component of the business	102	179
Cash paid for net assets related to acquisitions	(2,478)	-
Software developed for internal use	-	(123)
Software development costs capitalized	(818)	(807)
Net cash used in investing activities	$ (3,629)	$ (962)
Financing activities:		
Borrowings (repayments) under line of credit	180	(245)
Payments on long-term debt	(501)	(417)
Borrowings under long-term debt	1,500	-
Payments of capital lease obligations	(84)	(70)
Proceeds from issuance of common stock	9	12
Net cash provided by (used in) financing activities	$ 1,104	$ (720)
Effect of foreign currency exchange rate changes on	(12)	14

cash		
Net change in cash and cash equivalents	(1,160)	(293)
Cash and cash equivalents at beginning of period	1,350	1,134
Cash and cash equivalents at end of period	$ 190	$ 841
Cash paid for interest	$ 270	66
Cash paid for income taxes	$ 29	14
Noncash investing and financing activities		
Issuance of common stock in connection with acquisitions	$ 101	$ -
Debt issued in connection with acquisitions	3,000	-
Accrued liabilities assumed in connection with acquisitions	4,728	-
Issuance of common stock in connection with debt issuance and loan fees	623	-
Issuance of common stock related to payment of director compensation	140	-
Issuance of common stock related to payment of	108	12

executive compensation		
Contingent liabilities incurred in connection with acquisition	749	-

See accompanying notes

Notes to Unaudited Consolidated Financial Statements

1. Description of the Business and Significant Accounting Policies

Description of the Business

ARI Network Services, Inc. (“ARI” or the “Company”) provides technology-enabled services that help our customers effectively and efficiently sell more whole goods, parts, garments and accessories (“PG&A”). Our customer base of more than 22,000 dealers, 195 distributors, and 140 manufacturers utilize ARI’s products and services to drive and manage leads, efficiently service consumers at the parts counter, and enable eCommerce sales of PG&A. ARI’s solutions are aimed at markets with complex equipment requiring service and sold through an independent dealer channel and including the outdoor power, powersports, marine, RV, automotive wheel and tire, and white goods markets.

Most of our solutions leverage our library of electronic content that we have published and aggregated into a large content management system, which contains data related to more than 10 million active parts across more than 469,000 models; more than 500,000 active accessories; SKUs across more than 73,000 active products; more than 300 actively updated whole goods brands; and holds full model data and images for more than 175,000 active models.

We market our products primarily through software-as-a-service (“SaaS”) and data-as-a-service (“DaaS”) business models that typically contain both an annual auto-renewing subscription component as well as a variable usage-based revenue component. It is the nature of our products, along with the content and the continual management and updating of the content, which allows us to sell the majority of our products and services in a recurring revenue model. Today, more than 85% of our revenues are recurring.

We were incorporated in Wisconsin in 1981. Our principal executive office and headquarters is located in Milwaukee, Wisconsin. The office address is 10850 West Park Place, Suite 1200, Milwaukee, WI 53224, and our

telephone number at that location is (414) 973-4300. Our principal website address is www.arinet.com. ARI also maintains operations in Duluth, Minnesota; Cypress, California; Virginia Beach, Virginia; Floyds Knobs, Indiana; and The Netherlands.

Basis of Presentation

These consolidated financial statements include the financial statements of ARI and its wholly-owned subsidiaries. We eliminated all significant intercompany balances and transactions in consolidation. Any other adjustments deemed necessary by management for a fair presentation of all periods presented have been reflected as required by Regulation S-X, Rule 8-03, in the normal course of business.

Significant Accounting Policies

Our accounting policies are fully described in the footnotes to our Consolidated Financial Statements for the fiscal year ended July 31, 2012, which appear in our Annual Report on Form 10-K filed with the Securities and Exchange Commission on October 29, 2012. There were no changes to our accounting policies during the six months ended January 31, 2013.

Revenue Recognition

Revenue from software licenses, annual or periodic maintenance fees and catalog subscription fees, which are included in multiple element arrangements, are all recognized ratably over the contractual term of the arrangement, as vendor specific objective evidence does not exist for these elements. ARI considers all arrangements with payment terms extending beyond twelve months not to be fixed or determinable and evaluates other arrangements with payment terms longer than normal to determine whether the arrangement is fixed or determinable. If the fee is not fixed or determinable, revenue is recognized as payments become due from the customer. Arrangements that include acceptance terms beyond the standard terms are not recognized until acceptance has occurred. If collectability is not considered probable, revenue is recognized when the fee is collected.

Revenue for use of the network and for information services is recognized on a straight-line basis over the period of the contract.

Arrangements that include professional services are evaluated to determine whether those services are essential to the functionality of other elements of the arrangement. Types of services that are considered essential to software license arrangements include customizing complex features and functionality in a product’s base software code or developing complex interfaces within a customer’s environment. Professional services revenue for set-up and integration of hosted websites, or other services considered essential to the functionality of other elements of this type of arrangement, is amortized over the term of the contract. When professional services are not considered essential, the revenue allocable to the professional services is recognized pursuant to contract accounting using the percentage-of-completion method with progress-to-completion measured based upon labor hours incurred. When the current estimates of total contract revenue and contract cost indicate a loss, a provision for the entire loss on the contract is made in the period the amount is determined.

Revenue for variable transaction fees, primarily for use of the shopping cart feature of our websites, is recognized as it is earned.

Amounts invoiced to customers prior to recognition as revenue, as discussed above, are reflected in the accompanying balance sheets as deferred revenue.

Amounts received for shipping and handling fees are reflected in revenue. Costs incurred for shipping and handling are reported in cost of revenue.

Trade Receivables, Credit Policy and Allowance for Doubtful Accounts

Trade receivables are uncollateralized customer obligations due on normal trade terms, most of which require payment within thirty (30) days from the invoice date. Payments of trade receivables are allocated to the specific invoices identified on the customer's remittance advice or, if unspecified, are applied to the earliest unpaid invoices.

The carrying amount of trade receivables is reduced by an allowance that reflects management's best estimate of the amounts that will not be collected. Management individually reviews receivable balances that exceed ninety (90) days from the invoice date and, based on an assessment of current creditworthiness, estimates the portion of the balance that will not be collected. The allowance for potential doubtful accounts is reflected as an offset to trade receivables in the accompanying balance sheets.

Capitalized and Purchased Software Product Costs

Certain software development and acquisition costs are capitalized when incurred. Capitalization of these costs begins upon the establishment of technological feasibility. The establishment of technological feasibility and the on-going assessment of recoverability of software costs require considerable judgment by management with respect to certain external factors, including, but not limited to, the determination of technological feasibility, anticipated future gross revenue, estimated economic life and changes in software and hardware technologies.

The annual amortization of software products is the greater of the amount computed using: (a) the ratio that current gross revenue for the network or a software product bears to the total of current and anticipated future gross revenue for the network or a software product, or (b) the straight-line method over the estimated economic life of the product which currently runs from three to five years. Amortization starts when the product is available for general release to customers. All other software development and support expenditures are charged to expense in the period incurred.

Legal Provisions

ARI is periodically involved in legal proceedings arising from contracts, patents or other matters in the normal course of business. We reserve for any material estimated losses if the outcome is probable and can be reasonably estimated. We had no legal provisions for the three or six months ended January 31, 2013 and 2012.

Deferred Loan Fees and Debt Discounts

Fees associated with securing debt are capitalized and included in other long term assets on the balance sheet. Stock issued in connection with securing debt is recorded to debt discount, reducing the carrying amount of the debt on the balance sheet. Deferred loan fees and debt discounts are amortized to interest expense over the life of the debt.

2. Basic and Diluted Net Income per Share

Basic net income per common share is computed by dividing net income by the basic weighted average number of common shares outstanding during the period. Diluted net income per common share is computed by dividing net income by the weighted average number of common shares outstanding during the period and reflects the potential dilution that could occur if all of the Company’s outstanding stock options that have a strike price below the market price were exercised (calculated using the treasury stock method).

The following table is a reconciliation of basic and diluted net income per common share for the periods indicated (in thousands, except per share data):

	Three months ended January 31		Six months ended January 31	
	2013	2012	2013	2012

Net income	$ 4	$ 61	$ 117	$ 333
Weighted-average common shares outstanding	8,528	8,006	8,325	7,966
Effect of dilutive stock options and warrants	231	50	173	50
Diluted weighted-average common shares outstanding	8,759	8,056	8,498	8,016
Earnings per share				
Basic	$ 0.00	$ 0.01	$ 0.01	$ 0.04
Diluted	$ 0.00	$ 0.01	$ 0.01	$ 0.04
Options and warrants that could potentially dilute net income per share in the future that are not included in the computation of diluted net income per share, as their impact is anti-dilutive	280	823	735	823

3. Stock-based Compensation Plans

Stock Option Plans

We used the Black-Scholes model to value stock options granted. Expected volatility is based on historical volatility of the Company’s stock. The expected life of options granted represents the period of time that options granted are expected to be outstanding. The risk-free rate for periods within the contractual term of the options is based on the United States Treasury yields in effect at the time of grant.

As recognizing stock-based compensation expense is based on awards ultimately expected to vest, the amount of recognized expense has been reduced for estimated forfeitures based on the Company's historical experience. Total stock compensation expense recognized by the Company was approximately $48,000 and $27,000 during the three month periods ended January 31, 2013 and 2012, respectively, and $85,000 and $43,000 for the six month periods ended January 31, 2013 and 2012, respectively. There was approximately $232,000 and $164,000 of total unrecognized compensation costs related to non-vested options granted under the Company's stock option plans as of January 31, 2013 and July 31, 2012, respectively. There were no capitalized stock-based compensation costs at January 31, 2013 or July 31, 2012.

The fair value of each option granted was estimated in the period of issuance using the assumptions in the following table for the three and six month periods ended January 31, 2013 and 2012, respectively:

	Three months ended January 31		Six months ended January 31	
	2013	2012	2013	2012
Expected life (years)	10 years	10 years	10 years	10 years
Risk-free interest rate	1.7 %	2.0 %	1.7 %	2.1 %
Expected volatility	130.6 %	125.5 %	130.5 %	123.9 %
Expected forfeiture rate	11.7 %	24.8 %	13.5 %	21.2 %
Expected dividend yield	- %	- %	- %	- %
Weighted-average estimated fair value of options granted during the year	$ 1.29	$ 1.04	$ 1.25	$ 0.96

2000 Stock Option Plan

The Company's 2000 Stock Option Plan (the "2000 Plan") had 1,950,000 shares of common stock authorized for issuance. Each incentive stock option that was granted under the 2000 Plan is exercisable for a period of not more than ten years from the date of grant (five years in the case of a participant who is a 10% shareholder of the Company, unless the stock options are nonqualified), or such shorter period as determined by the Compensation Committee, and shall lapse upon the expiration of said period, or earlier upon termination of the participant's employment with the Company. The 2000 Plan expired on December 13, 2010, at which time it was terminated except for outstanding options. As a result, no new options may be granted under the 2000 Plan. Changes in option shares under the 2000 Plan during the three and six months ended January 31, 2013 and 2012 are as follows:

	Number of Options	Wtd. Avg. Exercise	Wtd. Avg. Remaining Contractual	Aggregate Instrinsic Value

		Price	Period (Years)	
Outstanding at 10/31/11	1,173,594	$ 1.37	5.82	$ 90,116
Granted	-	n/a	n/a	n/a
Exercised	(7,750)	0.65	n/a	n/a
Forfeited	(8,575)	0.85	n/a	n/a
Outstanding at 1/31/12	1,157,269	$ 1.38	5.59	$ 298,444
Exercisable at 1/31/12	981,552	$ 1.50	5.10	$ 167,097

Outstanding at 10/31/12	1,002,461	$ 1.40	4.97	$ 114,006
Granted	-	n/a	n/a	n/a
Exercised	(2,000)	0.35	n/a	n/a
Forfeited	(2,500)	0.73	n/a	n/a
Outstanding at 1/31/13	997,961	$ 1.41	4.72	$ 459,617
Exercisable at 1/31/13	922,374	$ 1.47	4.72	$ 375,251

	Number of Options	Wtd. Avg. Exercise Price	Wtd. Avg. Remaining Contractual Period (Years)	Aggregate Instrinsic Value
Outstanding at 7/31/11	1,236,333	$ 1.36	6.10	$ 34,041
Granted	-	n/a	n/a	n/a
Exercised	(20,950)	0.63	n/a	n/a
Forfeited	(58,114)	1.19	n/a	n/a
Outstanding at 1/31/12	1,157,269	$ 1.38	5.59	$ 298,444
Exercisable at 1/31/12	981,552	$ 1.50	5.10	$ 167,097

Outstanding at 7/31/12	1,099,769	$ 1.41	5.06	$ 105,849
Granted	-	n/a	n/a	n/a
Exercised	(12,800)	0.54	n/a	n/a
Forfeited	(89,008)	1.56	n/a	n/a
Outstanding at 1/31/13	997,961	$ 1.41	4.72	$ 459,617
Exercisable at 1/31/13	922,374	$ 1.47	4.72	$ 375,251

The range of exercise prices for options outstanding under the 2000 Plan was $0.15 to $2.74 at January 31, 2013 and 2012.

Changes in the 2000 Plan's non-vested option shares included in the outstanding shares above during the three and six months ended January 31, 2013 and 2012 are as follows:

	Number of Options	Wtd. Avg. Exercise Price
Non-vested at 10/31/11	179,467	$ 0.75
Granted	-	n/a
Vested	(250)	0.86
Forfeited	(3,500)	0.80
Non-vested at 1/31/12	175,717	$ 0.75
Non-vested at 10/31/12	75,587	$ 0.68
Granted	-	n/a
Vested	-	n/a
Forfeited	-	n/a
Non-vested at 1/31/13	75,587	$ 0.68

	Number of Options	Wtd. Avg. Exercise Price
Non-vested at 7/31/11	181,092	$ 0.75
Granted	-	n/a
Vested	(250)	0.86
Forfeited	(5,125)	0.80
Non-vested at 1/31/12	175,717	$ 0.75
Non-vested at 7/31/12	78,087	$ 0.69
Granted	-	n/a
Vested	-	n/a
Forfeited	(2,500)	0.73
Non-vested at 1/31/13	75,587	$ 0.68

The weighted average remaining vesting period was .87 and 1.24 years at January 31, 2013 and 2012, respectively.

2010 Equity Incentive Plan

The Board of Directors adopted the ARI Network Services, Inc. 2010 Equity Incentive Plan (the “2010 Plan”) on November 9, 2010, and the plan was approved by the Company's shareholders in December 2010. The 2010 Plan is the successor to the Company’s 2000 Plan.

The 2010 Plan includes the following provisions:

- the aggregate number of shares of Common Stock subject to the 2010 Plan is 650,000 shares;
- the exercise price for options and stock appreciation rights cannot be less than 100% of the fair market value, as defined, of the Company’s Common Stock on the date of grant;
- the exercise prices for options and stock appreciation rights cannot be repriced without shareholder approval, except to reflect changes to the capital structure of the Company as described in the 2010 Plan;
- a maximum term of ten (10) years for options and stock appreciation rights;
- a maximum of 325,000 of the shares available for issuance under the 2010 Plan can be in the form of restricted shares or restricted stock units, and the 2010 Plan does not have liberal share counting provisions (such as provisions that would permit shares withheld for payment of taxes or the exercise price of stock options to be re-granted under the plan); and
- awards cannot be transferred to third parties, with the exception of certain estate planning transfers, which can be made if the committee that administers the 2010 Plan approves such transfers.

Changes in option shares under the 2010 Plan during the three and six months ended January 31, 2013 and 2012 are as follows:

	Number of Options	Wtd. Avg. Exercise Price	Wtd. Avg. Remaining Contractual Period (Years)	Aggregate Instrinsic Value
Outstanding at 10/31/11	117,875	$ 0.75	9.67	$ 23,096
Granted	146,667	1.08	n/a	n/a
Exercised	-	n/a	n/a	n/a
Forfeited	(4,625)	0.61	n/a	n/a
Outstanding at 1/31/12	259,917	$ 0.94	9.65	$ 145,492
Exercisable at 1/31/12	21,188	$ 0.66	9.11	$ 17,838
Outstanding at 10/31/12	324,167	$ 1.10	9.09	$ 57,070
Granted	125,668	1.34	n/a	n/a
Exercised	-	n/a	n/a	n/a
Forfeited	(500)	0.65	n/a	n/a
Outstanding at 1/31/13	449,335	$ 1.17	9.11	$ 284,393
Exercisable at 1/31/13	111,460	$ 1.09	9.11	$ 79,585

	Number of Options	Wtd. Avg. Exercise Price	Wtd. Avg. Remaining Contractual Period (Years)	Aggregate Instrinsic Value
Outstanding at 7/31/11	54,250	$ 0.67	9.64	$ 5,570
Granted	210,667	1.00	n/a	n/a
Exercised	-	n/a	n/a	n/a
Forfeited	(5,000)	0.61	n/a	n/a
Outstanding at 1/31/12	259,917	$ 0.94	9.65	$ 145,492
Exercisable at 1/31/12	21,188	$ 0.66	9.11	$ 17,838
Outstanding at 7/31/12	310,667	$ 1.10	9.28	$ 41,962
Granted	145,668	1.29	n/a	n/a
Exercised	(3,000)	0.66	n/a	n/a
Forfeited	(4,000)	0.66	n/a	n/a
Outstanding at 1/31/13	449,335	$ 1.17	9.11	$ 284,393
Exercisable at 1/31/13	111,460	$ 1.09	9.11	$ 79,585

The range of exercise prices for options outstanding under the 2010 Plan was $.575 to $1.70 and $0.575 to $0.922 at January 31, 2013 and 2012, respectively.

Changes in the 2010 Plan's non-vested option shares included in the outstanding shares above during the three and six months ended January 31, 2013 and 2012 are as follows:

	Number of Options	Wtd. Avg. Exercise Price
Non-vested at 10/31/11	96,562	$ 0.78
Granted	146,667	1.08
Vested	-	-
Forfeited	(4,500)	0.61
Non-vested at 1/31/12	238,729	$ 0.97
Non-vested at 10/31/12	212,457	$ 1.11
Granted	125,668	1.34
Vested	-	n/a
Forfeited	(250)	0.65
Non-vested at 1/31/13	337,875	$ 1.19

	Number of Options	Wtd. Avg. Exercise Price
Non-vested at 7/31/11	32,937	$ 0.67
Granted	210,667	1.00
Vested	-	-
Forfeited	(4,875)	0.61
Non-vested at 1/31/12	238,729	$ 0.97
Non-vested at 7/31/12	192,707	$ 1.12
Granted	145,668	1.29
Vested	-	n/a
Forfeited	(500)	0.65
Non-vested at 1/31/13	337,875	$ 1.19

The weighted average remaining vesting period was 1.61 and 1.92 years at January 31, 2013 and 2012, respectively.

Restricted Stock

During the three months ended January 31, 2013, the Company granted an aggregate of 161,084 shares of restricted stock to certain executive officers, directors and employees under the 2010 plan, 72,000 shares of which will vest one year from the date of grant, and the balance of which vested on the date of grant, subject to 30-day restrictions on transfer. During the three months ended January 31, 2013, 18,000 shares of restricted stock with a grant date fair value of $22,000 were issued under the 2010 Plan as a discretionary bonus to an executive of the Company. The Company used the Black-Scholes model to value the grant with the following assumptions: risk-free interest rate of 1.75%; expected volatility of 1.3010%, expected forfeiture rate of 21.98% and expected dividend yield of 0%. The shares vest as follows: 4,500 shares vested immediately; 4,500 shares vest on July 31, 2013; 4,500 shares vest on July 31, 2014; and 4,500 shares vest on July 31, 2015. No restricted shares were issued during the three and six month periods ended January 31, 2012.

Employee Stock Purchase Plan

The Company's 2000 Employee Stock Purchase Plan, as amended, ("ESPP") has 225,000 shares of common stock reserved for issuance, of which 200,311 and 185,156 of the shares have been issued as of January 31, 2013 and July 31, 2012, respectively. All employees with at least nine months of service are eligible to participate. Shares may be purchased at the end of a specified period at the lower of 85% of the market value at the beginning or end of the specified period through accumulation of payroll deductions, not to exceed 5,000 shares per employee per year.

4. Other Intangible Assets

Amortizable intangible assets include customer relationships, trade names and employee non-compete agreements. Amortizable intangible assets are composed of the following at January 31, 2013 and July 31, 2012 (in thousands):

	Customer Relationships	Trade Names	Total
Net value 7/31/11	1,902	139	2,041
Amortization	(552)	(50)	(602)
Net value 7/31/12	$ 1,350	$ 89	1,439
Additions	3,060	130	3,190
Amortization	(199)	(36)	(235)

Net value 1/31/13	$ 4,211	$ 183	$ 4,394
Weighted average remaining useful life	11.94	1.63	11.51

The estimated amortization expense related to intangible assets for the years subsequent to January 31, 2013 is as follows (in thousands):

2013	$ 295
2014	587
2015	506
2016	485
2017	414
Thereafter	2,107
	$ 4,394

5. Debt

On July 27, 2011, the Company entered into a Loan and Security Agreement (the "Loan and Security Agreement") with Fifth Third Bank ("Fifth Third"). Pursuant to the terms of the Loan and Security Agreement, Fifth Third extended to the Company Credit Facilities consisting of a $1,500,000 revolving credit facility (the "Revolving Loan") and a $5,000,000 term loan facility (the "Term Loan" and, together with the Revolving Loan, the "Credit Facilities").

On August 17, 2012, the Credit Facilities were amended to increase the principal amount of the Term Loan by $1,000,000, and extend the maturity date to December 15, 2014. In connection with the amendment to the Credit Facility, the Company incurred $40,000 of debt closing costs, included in prepaid and other on the balance sheet and which are being amortized to interest expense over the term of the debt. Each of the Credit Facilities bears interest at a rate based on the one, two, three or six month LIBOR (as selected by the Company on the last business day of each month) plus 4.0% (effective rate of 4.25% as of January 31, 2013). There was $180,000 outstanding and $1,280,000 available on the Revolving Loan as of January 31, 2013.

On November 28, 2012 the Credit Facilities were further amended to waive the provisions of the Agreement that would prohibit ARI's acquisition of 50 Below and financing $3,500,000 of the acquisition with a secured subordinated promissory note in the same amount. Under the amendment, Fifth Third consented to the acquisition of the 50 Below assets and the related transactions and provided waivers of certain provisions of the Credit Facilities, subject to certain terms and conditions. Such terms and conditions include, among others, amendments to the fixed charge coverage ratio (0.90x for the four fiscal quarter period ending January 31, 2013) and senior leverage (maximum senior funded debt to EBITDA) ratio (1.75x for the fiscal quarter ending January 31, 2013) financial covenants and the addition of a maximum total funded debt to EBITDA ratio financial covenant (2.50x for the four fiscal quarter period ending January 31, 2013); amendment of the revolving loan and term loan maturity dates from July 27, 2014 to December 15, 2013; and other customary terms and conditions.

On March 8, 2013 the Loan and Security Agreement was further amended as described below in Note 11- Subsequent Events.

The Loan and Security Agreement contains covenants that restrict, among other things and subject to certain conditions, the ability of the Company to incur new debt, create liens on its assets, make certain investments, enter into merger transactions, issue capital securities (other than employee and director options, employee benefit plans, and other compensation programs), and make distributions to its shareholders. The Loan and Security Agreement also contains customary events of default which, if triggered, could result in an acceleration of the Company's obligations under the Loan and Security Agreement. The Credit Facilities are secured by a first priority security interest in substantially all assets of the Company and by a first priority pledge of all outstanding equity securities of each of the Company's domestic subsidiaries and 65% of outstanding equity securities of the Company's foreign subsidiaries.

Principal and interest on the Term Loan will be repaid in fixed monthly principal installments of $83,333 plus accrued but unpaid interest on the unpaid principal balance, with a final balloon payment due December 15, 2013. Mandatory prepayments of the Credit Facilities will be required in the amount of 50% of the Company's excess cash flow for each six-month period ending January 31 and July 31 until the debt is paid in full. Excess cash flow is defined as the remainder of net income plus interest, taxes, depreciation and amortization expense for such period, minus cash taxes paid, capital expenditures incurred, capitalized software costs and scheduled payments of principal and interest charges.

On November 28, 2012, the Company issued a Secured Non-Negotiable Subordinated Promissory Note (the "Sifen Note") to Michael D. Sifen, Inc. (the "Holder"), an affiliate of an existing shareholder of the Company, in aggregate principal amount of $3.5 million, the proceeds of which were used to partially fund the 50 Below acquisition. Interest accrues on the outstanding unpaid principal under the Sifen Note from and after November 7, 2012 until November 28, 2013 at a rate of 10.0% per annum, and at a rate of 14.0% per annum thereafter. Accrued interest only will be payable quarterly commencing on February 28, 2013 and continuing on each May 31st, August 31st, November 30th and February 28th thereafter until May 28, 2016, at which time all accrued interest and outstanding principal will be due and payable in full. The Sifen Note may be prepaid in part or in full at any time without premium or penalty. The Sifen Note contains negative covenants relating to, among other things, the Company's incurrence of future indebtedness and liens and the making of dividends and distributions upon shares of the

Company's capital stock, as well as customary events of default. As partial consideration for the Sifen Note, the Company issued 440,000 shares of the Company's common stock to the Holder valued at approximately $585,000, which is recorded to debt discount on the balance sheet as a reduction to long-term debt and amortized to interest expense over the life of the note.

The Sifen Note is subordinated in right of payment to all of the Company's existing indebtedness to Fifth Third and, subject to certain conditions, to all future indebtedness incurred to the Company's senior lenders, including to Fifth Third pursuant to the Credit Facilities. The Sifen Note is secured under a subordinated security agreement between the Holder and the Company by a security interest in substantially all of the Company's assets, subordinate to the security interests of Fifth Third and, subject to certain conditions, to all future senior debt incurred by the Company.

The following table sets forth certain information related to the Company's long-term debt, derived from our unaudited balance sheet as of January 31, 2013 and audited balance sheet as of July 31, 2012 (in thousands):

	January 31 2013	July 31 2012
Notes payable principal	$ 7,969	$ 3,972
Less debt discount	(557)	-
Less current maturities	(4,469)	(1,084)
Notes payable - non-current	$ 2,943	$ 2,888

6. Shareholder Rights Plan

On August 7, 2003, the Company adopted a Shareholder Rights Plan designed to protect the interests of common shareholders from an inadequate or unfair takeover, but not affect a takeover proposal which the Board of Directors believes is fair to all shareholders. Under the Shareholder Rights Plan adopted by the Board of Directors, as amended, all shareholders of record on August 18, 2003 received one Preferred Share Purchase Right for each share of common stock they owned. These Rights trade in tandem with the common stock until and unless they are triggered. Except as permitted pursuant to amendments to the Shareholder Rights Plan from time to time, s hould a person or group acquire more than 10% of ARI's common stock (or if an existing holder of 10% or more of the common stock were to increase its position by more than 1%), the Rights would become exercisable for every shareholder except the acquirer that triggered the exercise. The Rights, if triggered, would give the rest of the shareholders the ability to purchase additional stock of ARI at a substantial discount. The Rights will expire on August 18, 2013, and can be redeemed by the Company for $0.01 per Right at any time prior to a person or group becoming a 10% shareholder.

7. Income Taxes

The unaudited provision for income taxes for the three and six months ended January 31, 2013 and 2012 is composed of the following (in thousands):

	Three months ended January 31		Six months ended January 31	
	2013	2012	2013	2012
Current:				
Federal	$ (22)	$ -	$ (21)	$ -
State	(15)	4	(36)	(22)
Change in valuation allowance	941	21	941	21
Deferred, net	(69)	(86)	(174)	(228)
Income tax benefit (expense)	$ 835	$ (61)	$ 709	$ (229)

The provision for income taxes is based on taxes payable under currently enacted tax laws and an analysis of temporary differences between the book and tax bases of the Company’s assets and liabilities, including various accruals, allowances,

depreciation and amortization, and does not represent current taxes due. The tax effect of these temporary differences and the estimated benefit from tax net operating losses are reported as deferred tax assets and liabilities in the balance sheet. The provision includes permanent differences for a true up related to incentive stock option expense and losses related to the Netherlands operation. We have unused net operating loss carry forwards for federal income tax purposes, and as a result, we generally only incur alternative minimum taxes at the federal level.

As of January 31, 2013, after deducting year to date taxable income, the Company had accumulated net operating loss carryforwards for federal and state tax purposes of approximately $9,129,000 and $5,520,000, respectively, which expire as follows:

Year ended July 31, *	Federal	State
2013	$ 1,293	$ 1,701
2014	-	482
2015	-	3,258
2019	843	4
2020	6,043	-
2024	4	-
2025	-	75
2030	946	-
	$ 9,129	$ 5,520

* Years not shown have no amounts that expire.

Reduced for current year to date taxable income.

An assessment is performed semi-annually of the likelihood that our net deferred tax assets will be realized from future taxable income. To the extent management believes it is more likely than not that some portion, or all, of the deferred tax asset will not be realized, a valuation allowance is established. This assessment is based on all available evidence, both positive and negative, in evaluating the likelihood of realizability. Issues considered in the assessment include future reversals of existing taxable temporary differences, estimates of future taxable income (exclusive of reversing temporary differences and carryforwards) and prudent tax planning strategies available in future periods. Because the ultimate realizability of deferred tax assets is highly subject to the outcome of future events, the amount established as a valuation allowance is considered to be a significant estimate that is subject to change in the near term. To the extent a valuation allowance is established or there is a change in the allowance during a period, the change is reflected with a corresponding increase or decrease in the tax provision in the Consolidated Statements of Income. We will continue to evaluate the realizability of our deferred tax assets on a semi-annual basis.

The Company recorded a benefit related to a net change in estimate on our valuation allowance of approximately $941,000, or $0.11 per basic and diluted share, and $21,000, or $0.00 per basic and diluted share, during the three months ended January 31, 2013 and 2012, respectively, as a result of our semi-annual evaluation of the likelihood that our net deferred tax assets will be realized from future taxable income. The gain recognized in fiscal 2013 was primarily due to the estimated increase in future taxable income related to the growth in our business and operational synergies as a result of the two acquisitions in fiscal 2013.

8. Business Segments

The Company's business segments are internally organized primarily by geographic location of the operating facilities. In accordance with GAAP regarding disclosures about business segments, the Company has segregated the Netherlands operation and the United States operations into separate reportable segments. Segment revenue for the Netherlands operation includes only revenue generated out of the Netherlands subsidiary and does not include rest of world revenue attributable to the United States operations.

The Company evaluates the performance of and allocates resources to each of the segments based on their operating results. Unaudited information concerning our operating business segments is as follows for the periods indicated (in thousands):

	Three months ended January 31, 2013			
	United States	Netherlands	Eliminations	Consolidated
Revenue - external customers	$ 7,304	$ 174	$ -	$ 7,478
Revenue - intercompany	54	7	(61) 1	-
Cost of revenue	1,688	94	(61) 1	1,721
Operating expense	6,179	144	-	6,323
Interest expense	269	36	(36) 2	269
Other expense (income)	(40)	-	36 2	(4)
Income (loss) before provision for income taxes	$ (738)	$ (93)	$ -	$ (831)

	Six months ended January 31, 2013			
	United States	Netherlands	Eliminations	Consolidated
Revenue - external customers	$ 13,071	$ 349	$ -	$ 13,420
Revenue - intercompany	125	14	(139) 1	-
Cost of revenue	3,074	194	(139) 1	3,129
Operating expense	10,271	283	-	10,554
Interest expense	337	53	(53) 2	337
Other expense (income)	(61)	-	53 2	(8)
Income (loss) before provision for income taxes	$ (425)	$ (167)	$ -	$ (592)

	As of January 31, 2013			
	United States	Netherlands	Eliminations	Consolidated
Total assets	$ 32,993	$ 192	$ (1,829) 3	$ 31,356

1 The Netherlands segment charges the United States segment for customer support services and the United States segment charges the Netherlands segment for software royalties.

2 The United States segment charges the Netherlands segment for interest on the intercompany loan at a rate of 4.25%.

3 Net intercompany loan due from the Netherlands.

	Three months ended January 31, 2012			
	United States	Netherlands	Eliminations	Consolidated
Revenue - external customers	$ 5,306	$ 195	$ -	$ 5,501
Revenue - intercompany	68	8	(76) 1	-
Cost of revenue	1,222	105	(76) 1	1,251
Operating expense	3,970	110	-	4,080
Interest expense	59	35	(35) 2	59
Other expense (income)	(45)	(1)	35 2	(11)
Income (loss) before provision for income taxes	$ 168	$ (46)	$ -	$ 122

	Six months ended January 31, 2012			
	United States	Netherlands	Eliminations	Consolidated
Revenue - external customers	$ 10,511	$ 400	$ -	$ 10,911
Revenue - intercompany	140	18	(158) 1	-
Cost of revenue	2,343	202	(158) 1	2,387
Operating expense	7,623	235	- -	7,858
Interest expense	121	75	(75) 2	121
Other expense (income)	(91)	(1)	75 2	(17)
Income (loss) before provision for income taxes	$ 655	$ (93)	$ -	$ 562

	As of July 31, 2012			
	United States	Netherlands	Eliminations	Consolidated
Total assets	$ 21,800	$ 258	$ (1,549) 3	$ 20,509

1 Netherlands segment charges the United States segment for customer support services and the United States segment charges the Netherland segment for software royalties.

2 The United States segment charges the Netherlands segment for interest on the intercompany loan at a rate of 8%.

3 Net intercompany loan due from the Netherlands.

9. Disposition of a Component of an Entity

On March 1, 2011, the Company entered into an Asset Purchase Agreement (the "Agreement") with Globalrange Corporation ("Globalrange"). Under the terms of the Agreement, the Company sold to Globalrange certain rights and assets relating to our electronic data interchange business for the agricultural chemicals industry (the "AgChem EDI Business"). Because the AgChem EDI Business was not a separate entity or reportable segment, the transaction was recorded as a disposition of a component of an entity.

As part of the purchase price for the AgChem EDI Business, Globalrange agreed to assume certain liabilities of ARI relating to the AgChem EDI Business, primarily consisting of unearned revenue (as defined in the Agreement). Globalrange will make earn-out payments to ARI annually over a four-year period following the closing date, with an initial pre-payment of $80,000. The amounts of such earn-out payments will be determined based on collections received by Globalrange relating to the AgChem EDI Business during such period, and will be subject to a floor and cap, in accordance with the terms of the Agreement.

The fair value of the earn-out was originally estimated at $580,000 less an imputed discount of $97,000, based on the present value of the estimated earn-out payments (the "Earn-out Receivable"), discounted at 14%, which was the prevailing rate of interest charged on the Company's debt at the time of the sale. The discount is amortized to interest income, which is included in other income on the consolidated statement of income, over the life of the earn-out.

An assessment of the expected future cash flows of the Earn-out Receivable is performed annually in the third fiscal quarter based on historical receipts over the previous twelve-month period. Changes in estimate and cash received in excess of expected cash receipts are recorded as a gain in other expense (income). The Company did not perform an

assessment during the periods ended January 31, 2013 and 2012.

The remaining earn-out receivable includes $60,000 in prepaid expenses and other and $72,000 in other long term assets on the unaudited balance sheet at January 31, 2013, with estimated receivables as follows:

Year Ending July 31,	
2013	$ 24
2014	86
2015	48
Total Estimated Payments	158
Less imputed interest	(26)
Present value of Earnout	$ 132

The following table shows changes in the earn-out receivable during the three and six months ended January 31, 2013 and 2012 respectively:

	Three months ended January 31		Six months ended January 31	
	2013	2012	2013	2012
Beginning Balance	$ 177	$ 314	$ 218	$ 384
Net receipts	(53)	(98)	(102)	(179)
Imputed interest recognized	8	12	16	23
Ending Balance	$ 132	$ 228	$ 132	$ 228

10. Business Combinations

On November 28, 2012, the Company, through a wholly-owned subsidiary, completed the acquisition of the assets of the Retail Services Division of Fifty Below Sales & Marketing, Inc. (“50 Below”), a leading provider of eCommerce websites in the powersports, automotive tire and wheel aftermarket, medical equipment and pool and spa industries, for a purchase price of $5.0 million and the assumption of contracts having deferred revenue (ongoing service

requirements for which ARI will not receive payment) valued in the amount of $4,642,000 pursuant to Sections 363 and 365 of the United States Bankruptcy Code. The Company did not assume any outstanding debtor-in-possession financing obligation; however, the Company agreed to: (a) cover claims held by certain employees against the estate of 50 Below, subject to a cap of $17,000; and (b) release any potential claim against 50 Below for alleged infringement of ARI's intellectual property rights.

The Company funded $1.5 million of the purchase price through a combination of the Company's operating cash flows and availability under its existing Credit Facilities, including a $900,000 earnest money payment made on October 29, 2012. The balance of the purchase price was funded through a Secured Non-Negotiable Subordinated Promissory Note dated as of the Closing Date (the "Note") issued to Michael D. Sifen, Inc., an affiliate of an existing shareholder of the Company, in aggregate principal amount of $3.5 million.

The following tables show the preliminary allocation of the purchase price (in thousands):

	Purchase Price
Cash	$ 1,500
Financed by note payable	3,500
Assumed liabilities	4,642
Purchase Price	$ 9,642

	Purchase Allocation
Prepaid expenses	$ 9
Furniture and equipment	106
Developed technology	950
Tradenames	130
Customer Relationships	2,180
Goodwill	6,267
Purchase Price Allocation	$ 9,642

Intangible assets include the fair value of tradenames with a useful life of 2 years and customer relationships with a useful life of 15 years. Goodwill of $6.3 million represents the additional benefits provided to the Company by the acquisition of 50 Below through operational synergies. The acquisition increases the Company’s portfolio of equipment dealer websites by 230% and is expected to accelerate ARI’s opportunity to drive organic growth through the cross selling of new products. It also provides entry into new, high growth markets, including automotive aftermarket and durable medical equipment. The combined customer benefits and operational efficiencies are expected to result in a stronger organization that can create more value for its customers, employees and shareholders than the sum of the stand alone business units. The Company expects to recognize future tax benefits related to the 50 Below goodwill of approximately $2.5 million. The Company’s results of operations for the three and six months ended January 31, 2013 include approximately $1.7 million of revenue and $771,000 of net loss before taxes related to 50 Below.

The following unaudited pro forma information for the six months ended January 31, 2013 reflects the historical results of both companies with pro forma adjustments as if the acquisition had occurred on August 1, 2012. The unaudited pro forma information for the six months ended January 31, 2012 reflects the historical results of operations of both companies, with pro forma adjustments as if the acquisition had occurred on August 1, 2011. The unaudited pro forma combined financial information does not reflect any cost savings, operating synergies, revenue enhancements or implementation costs that the combined company may achieve as a result of the acquisition. The unaudited pro forma financial information presented is for information purposes only and does not purport to represent what the Company's and 50 Below's financial position or results of operations would have been had the acquisition in fact occurred on such date or at the beginning of the period indicated, nor does it project the Company's

and 50 Below's financial position or results of operations for any future date or period.

	Six months ended January 31	
	2013	2012
Revenue	$ 16,622	$ 15,138
Net income (loss)	$ 250	$ (1,319)
Net income(loss) per common share:		
Basic	$ 0.03	$ (0.17)
Diluted	$ 0.03	$ (0.16)

Pro forma adjustments to net income include amortization costs related to internally developed technology costs and intangible assets, acquisition-related professional fees, interest expense on the debt incurred to acquire the assets of 50 Below and the related debt discount, and the tax effect of the historical 50 Below results of operations and the pro forma adjustments at an estimated tax rate of 40% as follows:

	Six months ended January 31	
	2013	2012
Amortization of internally developed technology	$ 35	$ 52
Amortization of intangible assets	67	100
Acquisition-related professional fees	(790)	-
Interest expense	172	259
Income tax benefit	(438)	(1,101)

On August 17, 2012, the Company acquired substantially all of the assets of Ready2Ride, Incorporated (“Ready2Ride”) pursuant to the terms of an Asset Purchase Agreement dated August 17, 2012. Ready2Ride markets aftermarket fitment data to the powersports industry, which furthers ARI’s differentiated content strategy and expands ARI’s product offerings into aftermarket PG&A.

Consideration for the acquisition included $500,000 in cash, 100,000 shares of the Company’s common stock and assumed liabilities totaling approximately $419,000. In addition, the Company will be required to pay (1) a contingent hold back purchase price not to exceed, in aggregate, $250,000 on or before August 17, 2013, contingent upon the occurrence of certain customer-related events as described in the Purchase Agreement; and (2) a contingent earn-out purchase price ranging from, in aggregate,$0 to $1,500,000, with estimated payments of $270,000, $266,000 and $266,000 based on estimated revenue on the first, second and third anniversaries of the closing of the acquisition The fair value of the contingent earn-out was calculated using the present value of future estimated revenue over the next three years, which is estimated at $500,000. The following table shows changes in the estimated earnout payable for the six months ended January 31, 2013 (in thousands):

Beginning Balance	$ -
Fair value of earnout payable	500
Net payments	-
Imputed interest recognized	73
Ending Balance	$ 573

The following table shows the balance of the estimated earnout payable at January 31, 2013 (in thousands):

Year Ending July 31,	
2013	$ -
2014	270
2015	266
2016	267
Total Estimated Payments	803
Less imputed interest	(230)
Present value of Earnout	$ 573

The following tables show the estimated fair value and the allocation of the purchase price (in thousands):

	Purchase Price
Cash- net	$ 478
Assumed liabilities	419
Holdback	250
Earnout	500
Common Stock	101
Purchase Price	$ 1,748

	Purchase Allocation
Accounts receivable	$ 43
Furniture and equipment	12
Unearned revenue	(86)
Developed technology	366
Customer Relationships	880
Goodwill	533
Purchase Price Allocation	$ 1,748

Intangible assets consist primarily of customer contracts and relationships with an estimated useful life of 16 years. Goodwill consists of operating synergies, vendor relationships, new sales territories and industries. The Company incurred legal fees of $55,000 for the three month period ended October 31, 2012 in connection with the Ready2Ride acquisition, which were included in general and administrative expense. We have evaluated and determined that the Ready2Ride assets acquired as described above do not constitute a business that is “significant” as defined in the applicable SEC regulations.

11. Subsequent Events

We evaluated whether any events or transactions occurred after the balance sheet date that would require recognition or disclosure in our financial statements in accordance with GAAP, and determined that there was an event that occurred after January 31, 2013, but prior to March 11, 2012, that will have an effect on the financial statements.

On March 8, 2013, the Company entered into the Third Amendment to the Loan and Security Agreement (as amended, the "Loan and Security Agreement").

Under the Loan Agreement Amendment, the Loan and Security Agreement was amended primarily for the following purposes: (i) to permit an additional add-back to EBITDA ("Adjusted EBITDA") for non-cash expenses limited to bonuses and board director fees paid in shares of the Company's common stock, provided that any conversion of non-cash expenses into cash payments will be permitted only with the prior written of Fifth Third; (ii) to amend the definition of EBITDA to permit additional add-backs for certain transaction expenses; (iii) to amend the fixed charge coverage ratio to be calculated based on Adjusted EBITDA, rather than EBITDA and to exclude certain extraordinary gains; (iv) to amend the required fixed charge coverage ratio for the four fiscal quarter periods ending January 31, 2013 and April 30, 2013 to 0.90x and 1.00x, respectively; (v) to require delivery of the personal financial statement of Roy W. Olivier within 120 days after the end of each calendar year; (vi) to restrict the Company's ability to enter into certain transactions without the prior written consent of Fifth Third, including, without limitation, certain change in control transactions, reclassifications, reorganizations and recapitalizations of the Company's Common Stock or any compulsory share exchange pursuant to which any of the Company's common stock is effectively converted into and exchanged for other securities, cash or property; and (vii) to permit the Company to use the net cash proceeds from an equity raise transaction (as described below) in excess of $1,500,000 for working capital or to prepay the outstanding principal balance under the Sifen Note.

The Loan Agreement Amendment also contains Fifth Third Bank's consent to the Company raising additional capital by selling and issuing additional equity securities, and waivers by Fifth Third of the provisions of the Loan and Security Agreement that would otherwise have prohibited such a transaction, subject to certain terms and conditions. Such terms and conditions include, among others, a deemed event of default under the Loan and Security Agreement in the event the Company does not raise at least $250,000 in net cash proceeds on or before May 15, 2013 or any portion of the first $1,500,000 of such net cash proceeds is not used to prepay the outstanding principal balance of the Term Loan (the "Mandatory Prepayment"); and payment of a nonrefundable fee of $100,000 in the event the Company does not raise at least $1,500,000 on or before May 15, 2013 or any portion of the such amount is not used to make the Mandatory Prepayment. The Loan Agreement Amendment also contains other terms and conditions customary for an agreement of this nature. The Company was required to pay a $30,000 amendment fee to Fifth Third Bank in connection with the Loan Agreement Amendment.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion of our results of operations and financial condition, including, without limitation, the section entitled "Fiscal 2013 Rest of Year and Fiscal 2014 Outlook", should be read together with our unaudited consolidated financial statements for the three and six months ended January 31, 2013 and 2012, including the notes thereto, which appear elsewhere in this quarterly report on Form 10-Q. All amounts are in thousands, except per share data. This discussion contains forward-looking statements regarding future events and our future results that are subject to the safe harbors created under the Securities Act of 1933 (the "Securities Act") and the Securities Exchange Act of 1934 (the "Exchange Act"). All statements other than statements of historical facts are statements that could be deemed to be forward-looking statements. These statements are based on current expectations, estimates, forecasts, and projections about the markets in which we operate and the beliefs and assumptions of our management. Words such as "expects," "anticipates," "targets," "goals," "projects," "intends," "plans," "believes," "seeks," "estimates," "endeavors," "strives," "may," such words, and similar expressions are intended to identify such forward-looking statements. In addition, any statements that refer to projections of our future financial performance, our anticipated growth and trends in our businesses, and other characterizations of future events or circumstances are forward-looking statements. Readers are cautioned that these forward-looking statements are only predictions and are subject to risks, uncertainties, and assumptions that are difficult to predict, estimate, or verify, including those identified in our annual report on Form 10-K for the year ended July 31, 2012, under "Item 1A. Risk Factors," in Part II, Item 1A of this report, and elsewhere herein. Therefore, actual results may differ materially and adversely from those expressed in any forward-looking statements. We undertake no obligation to revise or update any forward-looking statements for any reason.

Overview of Business

ARI provides technology-enabled services that help our customers effectively and efficiently sell more whole goods, parts, garments and accessories ("PG&A"). Our customer base of more than 22,000 dealers, 195 distributors, and 140 manufacturers utilize ARI's products and services to drive and manage leads, efficiently service consumers at the parts counter, and enable eCommerce sales of PG&A. ARI's solutions are aimed at markets with complex equipment requiring service and sold through an independent dealer channel, including the outdoor power, powersports, marine, RV, automotive wheel and tire, and white goods markets. We believe that we have a first or second place market

share position in each of our core vertical markets.

Most of our solutions leverage our library of electronic content that we have published and aggregated into a large content management system, which contains data related to more than 10 million active parts across more than 469,000 models; more than 500,000 active accessories; SKUs across more than 73,000 active products; more than 300 actively updated whole goods brands; and holds full model data and images for more than 175,000 active models. We believe that this library of electronic content is our single biggest differentiator and also the largest barrier to entry for potential new competitors.

We market our products primarily through software-as-a-service (“SaaS”) and data-as-a-service (“DaaS”) business models that typically contain both an annual auto-renewing subscription component as well as a variable usage-based revenue component. It is the nature of our products, along with the content and the continual management and updating of the content, which allows us to sell the majority of our products and services in a recurring revenue model. Today, more than 85% of our revenues are recurring (we refer to these as “recurring revenues”, or “RR”). We define recurring revenue as products and services that are SaaS or DaaS-based and renewable, including license fees, maintenance fees, catalog subscription fees and hosting fees. The majority of our customers are on contracts of twelve months or longer, and these contracts typically auto-renew for additional twelve-month terms. This provides us with advanced visibility into our future revenues and opportunities to sell additional services to our customers. Our recurring revenue model also emphasizes the importance of maintaining a low rate of customer churn, one of the key drivers of any recurring revenue, subscription-based business.

Our Solutions

Our solutions, which are designed to enable our dealer, distributor, and manufacturer customers to increase the efficiency of their parts and service counter operations and sell more whole goods, PG&A, are centered around three core offerings: (i) electronic catalogs; (ii) eCommerce-enabled websites; and (iii) lead generation and management.

Electronic Catalogs

Our electronic catalog solutions, which include our PartSmart®, PartSmart Web™, PartStream™, AccessoryStream™, and AccessorySmart™ products, leverage our industry-leading content database to allow distributors and dealers to view and interact with this information to efficiently support the sales and service of equipment. We believe that our catalog solution is the fastest and most efficient in the market, as it allows multi-line dealers to quickly access data for any of the brands serviced from within the software, allowing the dealer's parts and service operations to more quickly service and sell to its customers. This drives online sales, increases sales within the dealership, and improves customer satisfaction.

We market our eCatalog solutions through our inside sales team and "test drives" (dealer trials), and eCatalog revenues are generated through recurring SaaS, DaaS ,software license, and catalog subscriptions, as well as non-recurring software customization fees. We derived 51% of our revenues from our electronic catalog services in the six months ended January 31, 2013. Of these revenues approximately 96% were recurring revenues.

We believe that our library of electronic content, which is essentially the "engine" that drives most our products, is the broadest and deepest content database in the vertical markets we serve. ARI, through our acquisition of Ready2Ride, is the first to offer aftermarket fitment data to our dealers in the powersports industry, and we have exclusive electronic data arrangements with several of the largest outdoor power equipment manufacturers.

Website Solutions

Our eCommerce enabled website solutions, which are tailored to the vertical markets we serve, provide our dealer customers with a web presence that serves as a platform for driving leads and eCommerce sales. The sites allow consumers to obtain information about the dealership and its product lines and purchase OEM or aftermarket PG&A 24 hours a day, 7 days a week. We also offer a mobile solution that allows a dealer's website to be fully functional on smart mobile phones.

We market our websites through our inside sales team, who will provide live demos as part of the sales process. Websites generate revenues through recurring SaaS subscriptions, variable transaction fees for all eCommerce sales generated by the websites, and non-recurring setup and customization professional service fees. Website services accounted for approximately 35% of revenues in the six months ended January 31, 2013. Of these revenues approximately 90% were recurring revenues.

Historically, websites accounted for approximately 25% of ARI's total revenues. With the November 2012 acquisition of 50 Below, websites will become ARI's largest source of revenue. We currently host and maintain more than 5,500 websites for dealers in the outdoor power, powersports, automotive wheel and tire aftermarket, marine and RV markets.

Lead Management Solution

Our lead management solution, Footsteps™, is designed to allow our customers to efficiently manage and nurture generated leads, increasing conversion rates and ultimately revenues. Footsteps™ connects equipment manufacturers with their dealer channel through lead consolidation and distribution, and allows the dealers to handle leads more efficiently and professionally through marketing automation and business management system integration. The product provides a complete database of customers and prospects, and manages the dealer to customer relationship from generating email campaigns and automated responses, to providing sales teams with a daily follow-up calendar and reminder notices.

We market our lead management solution through our outside sales team and by providing free trial versions of the product. Once a customer has experienced the free trial version of the product our inside sales team attempts to up sell the customer into a premium version of the product. Our lead management product generates revenues through SaaS subscription fees and through variable usage-based fees for email campaigns performed through the software. We derived approximately 4% of our revenues from Footsteps™ in the six months ended January 31, 2013, most of which was recurring.

Lead Generation Service

Our lead generation service, SearchEngineSmart™, is designed to drive additional traffic to dealers' websites through optimization of the dealers' paid search engine marketing campaigns, which include optimization for results in our dealers' local areas. These services are typically sold as three-month service agreements, which do not auto-renew. Accordingly, we classify revenue from this service as non-recurring. We derived approximately 4% of our revenues from lead generation services in the six months ended January 31, 2013.

Other Services

We also offer a suite of complementary solutions, which include software and website customization services, website hosting, and document transfer and communication services. On a combined basis, these other services accounted for approximately 6% of revenue in the six months ended January 31, 2013. Of these revenues, approximately one-third are recurring. However, the percentage of other revenues classified as recurring will fluctuate from period to period based on the amount of professional fee revenues recognized for large-scale software customization projects.

Further information regarding our service offerings can be accessed at the Company's website at www.arinet.com, or in our Annual Report on Form 10-K for the year ended July 31, 2012. Please note that we are not including the information contained on or available through our website as a part of, or incorporating such information by reference into, this quarterly report on Form 10-Q.

Our Strategy

ARI's goal is to become the leading provider of SaaS and DaaS solutions that help our customers, in selected vertical markets, efficiently and effectively sell and service more whole goods and PG&A. We aim to grow revenues at a double-digit organic rate, and to grow earnings faster than revenues through scalability. We will provide our solutions to dealers, distributors, manufacturers, service providers, and consumers in vertical markets where the finished goods are complex equipment requiring service and are primarily sold through an independent dealer channel. We believe this strategy will drive increased value to our shareholders, employees, and customers.

We believe that execution of the following strategic foundations will enable us to achieve the growth and profitability needed to drive long-term sustainable value for our shareholders. These strategic foundations are primarily centered on enhancing the value proposition to our customers, which will lead to additional revenues through pricing actions, product and feature up sells, and reduced customer churn rates.

Drive organic growth through innovative new service offerings, differentiated content and geographic expansion

As a subscription-based, recurring revenue business, the most important drivers of future growth are adding new customers (referred to as new “logos”), increasing the level of our recurring revenue through new products and features as well as new markets, and reducing the rate of customer churn.

During the six months ended January 31, 2013 recurring revenues increased 25.6% compared to the same period last year, much of which was driven by the acquired 50 Below and Ready2Ride businesses. Excluding revenues attributable to the acquired businesses, comparable recurring revenues grew 4.5% year over year. At the product level, catalog recurring revenues grew organically by 2.0%; websites by 14.3%; and lead management revenues remained flat year over year. The continued increase in recurring revenues resulted from improvements in customer churn rates, which is discussed below, but was also driven by progress we made with respect to our organic growth strategy, which includes the following critical objectives:

· Develop and deploy innovative new solutions. We have resources assigned to each of our core products that continue to research and develop new value-added features and functionality in our existing products. The introduction of new solutions, upgrades to existing products, and new feature sets are all designed to grow our average revenue per dealer (“ARPD”), an important measure for a subscription-based business, and the increase in our customer base serves to quickly compound the benefits of an increased ARPD. In the first six months of fiscal 2013, we released numerous new product features and upgrades, including the rollout of our new AccessorySmart™ aftermarket parts lookup solution, a first of its kind in the powersports industry. AccessorySmart™ has received numerous accolades since its introduction, including a Nifty Fifty Award by Powersports Business as one of the upcoming products in the powersports industry. In addition to AccessorySmart™, we launched a website add-on that allows powersports dealers with a 50 Below website to post their inventory on Craigslist, eBay and Facebook.

- Expand geographically. Currently, only a small percentage of our revenues are generated from international operations. Our OEM customers have stated objectives to drive growth internationally, with a focus on the "BRIC" countries of Brazil, Russia, India, and China. We must continue to support our OEM customers with products and content for these markets. During the first half of fiscal 2013, we expanded our content offerings in the international outdoor power market and have begun to establish numerous relationships with OEMs in China. We have also begun to upgrade our product roadmaps to allow us to rapidly deploy our products in these markets in a scalable and efficient manner.
- Differentiate our content. We believe that we have the largest library of whole goods and PG&A content data in the vertical markets we serve. However, simply offering the largest content library in the markets we serve is not sufficient to drive the long-term growth we desire. We strive to deliver more value to our customers through enrichment of our content. Content enrichment can take several forms, including the incorporation of user reviews and feedback into our existing content, further enhancing content provided to us by our OEM customers, and creating new forms of content that further our customers' ability to efficiently service and sell more whole goods and PG&A. Our August 2012 acquisition of Ready2Ride expanded our content library to include aftermarket fitment data for the powersports industry, which is the only content of its type available electronically. We have already leveraged this content in our new AccessorySmart™ product, which was previously discussed.

Nurture and retain existing customers through world-class customer service and value-added product feature updates

In order to achieve sustained double-digit organic growth, we not only need to sell into new logos but just as importantly we must retain and renew existing customers. In a SaaS business, the cost to retain an existing customer is much less than the cost to acquire a new customer. Accordingly, customer churn (the rate at which existing customers exit) is one of the most important metrics we track and manage. We have experienced marked improvements in our churn rates the past several years as a result of strategic actions taken by the Company, all of which are designed to enhance the "stickiness" of our product within our customers' operations and have included: stabilization of our technology infrastructure through the use of a third party hosted data center; deployment of a state-of-of-the-art call center to support our inside sales, customer service and support teams; implementation of a renewal and retention team solely dedicated to ensuring our customers are satisfied and realizing the value proposition they expect from their spend with ARI; and numerous product features and upgrades.

In fiscal 2012, our rate of customer churn improved by 19% over fiscal 2011 and we have seen further improvement thus far in fiscal 2013. For the six months ended January 31, 2013, overall churn rates improved nearly 25% compared to the same period last year.

Lead the market with open integration to related platforms

One of our strategic advantages is our focus on integrating our solutions with dealer business management systems ("DMS") in order to pass key information, including customer and transactional data, between the systems, saving our

customers valuable time and eliminating redundant data entry. We currently have integration capabilities with over 90 DMS's (we refer to these relationships as "Compass Partners") and we continue to seek other strategic alliances that can be integrated with our product and service offerings. During the first half of fiscal 2013, ARI announced an integration of its WebSiteSmart™ product with CycleTrader.com, one of the top classified sites for the buying and selling of new and used motorcycles. This integration will allow ARI dealer customers to synchronize their inventory between their ARI website and CycleTrader.com.

Successfully execute acquisitions that align with our core strategy

Historically, acquisitions have been a significant driver of ARI's growth. A summary of our most recent acquisitions follows:

Acquisition	Date	Strategy
OC-Net, Inc.	Jan-07	New website product
Info Access	Jul-08	Market-leading entrance into appliances market
Channel Blade Technologies	Apr-09	Market-leading entrance into marine and RV markets New lead management product, Footsteps™
Ready2Ride, Inc.	Aug-12	First to market aftermarket fitment data to the Powersports industry
50 Below Sales & Marketing, Inc. (Retail Division)	Nov-12	A market leader in the powersports industry Entrance into automotive wheel and tire aftermarket, medical equipment and pool and spa industries New award-winning website product

Although we believe organic growth will be the primary driver of our business for the foreseeable future, we will continue to evaluate acquisitions that are in alignment with our core strategy.

Summary of Operating Results

On November 28, 2012, ARI acquired the assets of the retail division of 50 Below. 50 Below was one of ARI's leading competitors in the powersports industry and is a leading provider of eCommerce websites to more than 3,500 dealers in the powersports, automotive wheel and tire aftermarket, medical equipment, and pool and spa industries. Our second quarter operating results were heavily influenced by this acquisition, as the acquisition more than doubles the size of ARI's website business. Accordingly, our revenues for the three-month period ended January 31, 2013 reflect a 36% increase over the same period last year. Additionally, a significant amount of non-recurring legal and other professional fees were incurred executing the acquisition. As a result, we incurred an operating loss for the

quarter, versus operating income last year.

- Total revenue increased 35.9% or $1,977,000 for the three-month period ended January 31, 2013, compared to the same period last year. For the six months ended January 31, 2013, total revenue increased 23.0% or $2,509,000 compared to the same period last year. We recognized revenues of $1,669,000 in the quarter and year to date periods from 50 Below and $147,000 and $281,000 for the three and six month periods from Ready2Ride, our August 2012 acquisition.

- We incurred an operating loss of $566,000 in the quarter, versus operating income of $170,000 last year. For the six months ended January 31, 2013, we incurred an operating loss of $263,000, versus operating income of $666,000 for the same period last year. The fiscal 2013 operating losses are the result of acquisition-related legal and other professional fees of $623,000 and $838,000 that were expensed during the quarter and year to date periods, respectively.

- We reported net income during the quarter of $4,000, versus $61,000 last year. For the six months ended January 31, 2013, we reported net income of $117,000 versus $333,000 for the same period last year. The decline in net income for the quarter and year-to-date periods was primarily the result of the acquisition related legal and professional fees, ongoing acquisition integration costs, and increased interest expenses, which were in part offset by an income tax benefit related to a change in the valuation allowance.

· Cash flows from operations during the quarter were $1,288,000, versus $540,000 last year, and for the six months ended January 31, 2013 were $1,797,000 versus $1,375,000 for the same period a year ago. The increase in operating cash flows resulted from closely managing vendor payments during the integration of the Company's two acquisitions.

We expect our operating results for the remainder of fiscal 2013 to continue to be heavily influenced by our first quarter acquisition of Ready2Ride and our second quarter acquisition of 50 Below. Revenues for the remainder of the year will continue to significantly outpace fiscal 2012 as a result of these acquisitions; however, the legal and professional fees incurred will dampen our operating income.

Revenue

The following table summarizes our recurring and non-recurring revenue by major product category:

	Three months ended January 31			Six months ended January 31		
	2013	2012	Percent Change	2013	2012	Percent Change
Catalog						
Recurring revenue	$ 3,328	$ 3,153	5.6 %	$ 6,649	$ 6,245	6.5 %
Non-recurring revenue	107	234	(54.3) %	244	456	(46.5) %
Total catalog revenue	3,435	3,387	1.4 %	6,893	6,701	2.9 %
Percent of revenue recurring	96.9 %	93.1 %		96.5 %	93.2 %	
Website						
Recurring revenue	2,946	1,137	159.1 %	4,205	2,218	89.6 %
Non-recurring revenue	165	182	(9.3) %	429	424	1.2 %
Total website revenue	3,111	1,319	135.9 %	4,634	2,642	75.4 %
Percent of revenue recurring	94.7 %	86.2 %		90.7 %	84.0 %	
Lead management						
Recurring revenue	211	220	(4.1) %	423	425	(0.5) %
Non-recurring revenue	45	43	4.7 %	90	94	(4.3) %
Total lead management revenue	256	263	(2.7) %	513	519	(1.2) %
Percent of revenue recurring	82.4 %	83.7 %		82.5 %	81.9 %	
Lead generation						

Recurring revenue	-		-		-	%	-		-	%
Non-recurring revenue	276		261		5.7	%	583		453	28.7 %
Total lead generation revenue	276		261		5.7	%	583		453	28.7 %
Percent of revenue recurring	-	%	-	%			-	%	- %	
Other										
Recurring revenue	115		142		(19.0)	%	262		301	(13.0) %
Non-recurring revenue	285		129		120.9	%	535		295	81.4 %
Total catalog revenue	400		271		47.6	%	797		596	33.7 %
Percent of revenue recurring	28.8	%	52.4	%			32.9	%	50.5 %	
Total										
Recurring revenue	6,600		4,652		41.9	%	11,539		9,189	25.6 %
Non-recurring revenue	878		849		3.4	%	1,881		1,722	9.2 %
Total revenue	$ 7,478		$ 5,501		35.9	%	$ 13,420		$ 10,911	23.0 %
Percent of revenue recurring	88.3	%	84.6	%			86.0	%	84.2 %	

Total revenue increased 35.9% or $1,977,000 for the three months ended January 31, 2013, compared to the same period last year. Recurring revenue increased 41.9% or $1,948,000 for the three months ended January 31, 2013, compared to the same period last year. For the six months ended January 31, 2013, total revenues increased $2,509,000, or 23.0%, and recurring revenues increased $2,350,000, or 25.6%. The overall increase in revenue is attributed primarily to the two acquisitions. For the quarter ended January 31, 2013, revenues included in our results of operations attributable to 50 Below and Ready2Ride were $1,669,000 and $147,000, respectively, and for the six months ended January 31, 2013, revenues attributable to 50 Below and Ready2Ride were $1,669,000 and $281,000, respectively.

Year over year revenues, excluding revenues attributable to the acquired businesses, increased $165,000, or 3.0%, for the quarter ended January 31, 2013, and increased $563,000, or 5.2% for the six months ended January 31, 2013. Recurring revenues, excluding recurring revenues attributable to the acquired businesses, increased $136,000, or 3.0%, for the quarter and $404,000, or 4.4%, for the six months ended January 31, 2013. This increase is attributed to a continued decline in the Company's rate of customer churn, which has collectively led to continued growth in recurring revenue. For the six months ended January 31, 2013, our customer churn rates improved by nearly 25% over the same period last year.

Catalog

Catalog revenue is generated from catalog subscriptions, software license fees, license renewal fees, software maintenance and support fees and professional services related to data conversion. Revenue from the acquired Ready2Ride business is included in Catalog revenue. Catalog revenue increased $48,000 or 1.4% or for the three months ended January 31, 2013, compared to the same period last year, and increased $192,000 or 2.9% for the six months ended January 31, 2013.

Catalog recurring revenue increased $175,000 or 5.6% and $404,000 or 6.5% for the three and six-month periods ended January 31, 2013, respectively. Excluding the revenues attributable to Ready2Ride, these increases were 0.9% and 2.0%, respectively. Catalog has historically been ARI's largest source of revenue, but also the slowest growth revenue source. We expect organic catalog revenue growth to accelerate beginning in the third quarter and into fiscal 2014 as a result of the recently released new AccessorySmart™ product at the 2013 Dealer Expo in Indianapolis. AccessorySmart™, a fitment-powered aftermarket parts, garments, and accessories lookup solution, is the first of its kind in the powersports industry and recently won a "Nifty 50 Award" by Powersports Business.

We experienced a decline in the non-recurring portion of catalog revenues. Non-recurring revenues will fluctuate from quarter to quarter and from year to year due to the timing of large-scale software customization projects.

Website

Website revenue is generated from one-time set-up fees and recurring subscription fees on our website products, as well as transaction fees from customers' online sales generated via the websites. Website revenue increased $1,792,000 or 135.9% for the three-month period ended January 31, 2013, compared to the same period last year. For the six months ended January 31, 2013 website revenue increased $1,992,000 or 75.4%. This increase is primarily attributable to the addition of revenues from 50 Below, which generated revenues of $1,669,000 since the acquisition. Excluding the revenues from 50 Below, organic website recurring revenue growth was 12.7% and 14.5% for the three and six months ended January 31, 2013, when compared to their respective prior year periods.

As stated above, 50 Below's revenues from the date of acquisition until the end of the quarter were $1,669,000. On an annualized basis, the acquisition of the acquired 50 below business will more than double the size of ARI's website business and will make websites ARI's largest source of revenue going forward. In our Form 8-K/A filing dated February 11, 2013, ARI reported the audited results of operations of 50 Below for the fiscal years ended July 31, 2012 and 2011, and unaudited results for the quarter ended October 31, 2012. The acquired 50 Below business reported revenues of $8,811,000 and $7,792,000 for the fiscal years ended July 31, 2012 and 2011, respectively, and $2,401,000 for the three months ended October 31, 2012. When combined with ARI's website revenues, on a pro forma basis, websites would have been ARI's largest source of revenue for all reported periods.

Lead Management

Lead management revenue is generated from one-time set-up fees and recurring subscription fees for the use of the Company's Footsteps® products. Revenue from lead management products for the three and six months ended January 31, 2013 was $211,000 and $423,000, consistent with the same periods last year.

Lead Generation

Lead generation revenue is realized from the sale of the Company's SearchEngineSmart® ("SES") service and is non-recurring. Revenue from the Company's lead generation services increased $16,000 or 5.7% for the three months ended January 31, 2013 and $130,000 or 28.7% for the six months ended January 31, 2013, compared to the same periods last year. Revenue from the Company's lead generation services does not directly contribute to MRR growth, but contributes to MRR growth in the lead management and website services.

Other Revenue

Other revenue primarily consists of professional services related to software customization, website hosting fees, and revenue generated from other products that are ancillary to our three core offerings. Other revenue increased $129,000 or 47.6% for the three months ended January 31, 2013 and $201,000 or 33.7% for the six months ended January 31, 2013, compared to the same periods last year. Management anticipates that other revenue will fluctuate based on the timing of professional fees related to software customization.

Cost of Revenue and Gross Margin

We classify as cost of revenue those costs directly attributable to the provision of services. These costs include (i) software amortization, which represents the periodic amortization of costs for internally developed or purchased software sold to customers; (ii) direct labor for the provision of catalog production, product implementations and professional services revenue; and (iii) other direct costs, which represent amounts paid to third party vendors directly attributable to the services we provide our customers.

The table below breaks out cost of revenue into each of these three categories:

	Three months ended January 31				Six months ended January 31			
	2013	Percent of Revenue	2012	Percent of Revenue	2013	Percent of Revenue	2012	Percent of Revenue
Net revenues	$ 7,478		$ 5,501		$ 13,420		$ 10,911	
Cost of revenues:								
Amortization of capitalized software costs	464	6.2 %	350	6.4 %	860	6.4 %	685	6.3 %
Direct labor	566	7.6 %	388	7.1 %	1,014	7.6 %	772	7.1 %
Other direct costs	691	9.2 %	513	9.3 %	1,255	9.4 %	930	8.5 %
Total cost of revenues	1,721	23.0 %	1,251	22.7 %	3,129	23.3 %	2,387	21.9 %
Gross profit	$ 5,757	77.0 %	$ 4,250	77.3 %	$ 10,291	76.7 %	$ 8,524	78.1 %

Gross profit was $5,757,000 or 77.0% of revenue for the three months ended January 31, 2013, compared to $4,250,000 or 77.3% of revenue for the same period last year. For the six months ended January 31, 2013 gross profit was $10,291,000 or 76.7% of revenue compared to $8,524,000 or 78.1% of revenue for the same period last year. This decline in gross profit margin was primarily attributed to: (i) an increase in SES and professional services

revenues, which have a lower margin than our core recurring revenue products; and (ii) an increase in lead management software amortization related to Footsteps upgrades designed to spur future revenue growth for this product. The Company expects fluctuations in gross margin from quarter to quarter and year over year based on the mix of products sold, but expects its gross margins to improve over time as we focus our sales efforts on the higher margin, recurring revenue products.

The following table summarizes our gross profit and gross margin percentage by major product category:

	Three months ended			Six months ended		
	January 31 2013	2012	Percent Change	January 31 2013	2012	Percent Change
Catalog						
Revenue	$ 3,435	$ 3,387	1.4 %	$ 6,893	$ 6,701	2.9 %
Cost of revenue	497	482	3.1	974	971	0.3 %
Gross profit	2,938	2,905	1.1	5,919	5,730	3.3 %
Gross margin percentage	85.5 %	85.8 %		85.9 %	85.5 %	
Website						
Revenue	3,111	1,319	135.9	4,634	2,642	75.4 %
Cost of revenue	641	364	76.1	903	696	29.7 %
Gross profit	2,470	955	158.6	3,731	1,946	91.7 %
Gross margin percentage	79.4 %	72.4 %		80.5 %	73.7 %	
Lead management						
Revenue	256	263	(2.7)	513	519	(1.2) %
Cost of revenue	190	123	54.5	357	234	52.6 %
Gross profit	66	140	(52.9)	156	285	(45.3) %
Gross margin percentage	25.8 %	53.2 %		30.4 %	54.9 %	
Lead generation						
Revenue	276	261	5.7	583	453	28.7 %
Cost of revenue	233	214	8.9	504	354	42.4 %
Gross profit	43	47	(8.5)	79	99	(20.2) %
Gross margin percentage	15.6 %	18.0 %		13.6 %	21.9 %	
Other						
Revenue	400	271	47.6	797	596	33.7 %
Cost of revenue	160	68	135.3	391	132	196.2 %
Gross profit	240	203	18.2	406	464	(12.5) %
Gross margin percentage	60.0 %	74.9 %		50.9 %	77.9 %	
Total						
Revenue	7,478	5,501	35.9	13,420	10,911	23.0 %
Cost of revenue	1,721	1,251	37.6	3,129	2,387	31.1 %
Gross profit	$ 5,757	$ 4,250	35.5	$ 10,291	$ 8,524	20.7 %
Gross margin percentage	77.0 %	77.3 %		76.7 %	78.1 %	

Catalog

Catalog gross profit margins remained relatively stable year over year. Catalog margins are expected to gradually improve over time as the new AccessorySmart™ product ramps up.

Website

Website gross profit margin increased from 72.4% for the three months ended January 31, 2012 to 79.4% for the same period this year. For the six months ended January 31, 2013, website gross profit margin was 80.5%, compared to 73.7% for the same period last year. The Company expects to see website gross margins to continue to improve as recurring revenues increase and customer churn rates continue to decline.

Lead Management

Lead management gross profit margin decreased from 53.2% for the three months ended January 31, 2012 to 25.8% for the same period this year. For the six months ended January 31, 2013, lead management gross profit margin was 30.4%, compared to 54.9% for the same period last year. The decline in gross profit margin is due to an increase in software amortization related to Footsteps enhancements that are designed to spur future growth of this product.

Lead Generation

Lead generation gross profit margins are low relative to other ARI products as much of the revenue generated from this service is passed along to the search engine providers for the purchase of key words. While margins on our lead generation service are expected to remain low, there will be fluctuations from period to period based on periodic volume discounts.

Other Revenue

Gross profit margin on other revenue declined for the three and six months ended January 31, 2013, compared to the same periods last year primarily due to an increase in professional services revenue, which has a lower margin than our other products. The Company expects fluctuations in gross margin on other revenue, depending on the mix of products and services sold.

Operating Expenses

The following table summarizes our unaudited operating expenses by expense category:

	Three months ended January 31				
	2013	Percent of Revenue	2012	Percent of Revenue	Percent Change
Sales and marketing	$ 1,744	23.3 %	$ 1,118	20.3 %	56.0 %
Customer operations and support	1,470	19.7 %	850	15.5 %	72.9 %
Software development and technical support	672	9.0 %	490	8.9 %	37.1 %

General and administrative	2,098	28.1	%	1,218	22.1	%	72.2	%
Depreciation and amortization [1]	339	4.5	%	404	7.3	%	(16.1)	%
Net operating expenses	$ 6,323	84.6	%	$ 4,080	74.2	%	55.0	%

	Six months ended January 31							
	2013	Percent of Revenue		2012	Percent of Revenue		Percent Change	
Sales and marketing	$ 2,790	20.8	%	$ 2,151	19.7	%	29.7	%
Customer operations and support	2,478	18.5	%	1,696	15.5	%	46.1	%
Software development and technical support	1,249	9.3	%	878	8.0	%	42.3	%
General and administrative	3,418	25.5	%	2,326	21.3	%	46.9	%
Depreciation and amortization [1]	619	4.6	%	807	7.4	%	(23.3)	%
Net operating expenses	$ 10,554	78.6	%	$ 7,858	72.0	%	34.3	%

(1) Exclusive of amortization of software products of $464, $350, $860 and $685 for the three and six months ended January 31, 2013 and 2012, respectively, which are included

in cost of revenue.

Net operating expenses increased $2,243,000 or 55.0% and $2,696,000 or 34.3% for the three and six months ended January 31, 2013, compared to the same periods last year. The increase in operating expenses was primarily due to the acquisitions of Ready2Ride and 50 Below. Excluding the acquisitions, ARI’s comparable operating expenses would have increased $282,000 or 3.5% for the year to date period. For the three months ended January 31, 2013, ARI’s comparable expenses would have been flat year over year.

For the six months ended January 31, 2013, operating expenses of $2,065,000 were attributable to the 50 Below business. Of these, approximately $790,000 were acquisition-related legal and professional fees. Over the same period, operating expenses of $424,000 were attributable to the Ready2Ride business. Of these, approximately $50,000 were acquisition-related legal and professional fees.

Sales and Marketing Expenses

Sales and marketing expenses consist primarily of personnel and related costs, including commissions for our sales and marketing employees, and the cost of marketing programs and trade show attendance. Marketing programs consist of lead generation and direct marketing, advertising, events and meeting costs, public relations, brand building and product management activities. Sales and marketing expenses increased $535,000 or 47.9% for the three months ended January 31, 2013, compared to the same period last year, and increased $548,000 or 25.5% for the six months ended January 31, 2013, compared to the prior year period. Excluding expenses related to 50 Below and Ready2Ride, sales and marketing expenses increased 3.4% and 1.5% for the three and six months ended January 31, 2013, respectively.

Customer Operations and Support

Customer operations and support expenses are composed of our customer hosting operations, software maintenance agreements for our core network, and personnel and related costs for operations and support employees. Customer operations and support costs increased $534,000 or 62.8% for the three months ended January 31, 2013, compared to the same period last year, and increased $696,000 or 41.0% for the six months ended January 31, 2013, compared to the prior year period. Excluding expenses related to 50 Below and Ready2Ride, customer operations and support expenses increased 15.0% for the three and six months ended January 31, 2013, respectively. This increase is consistent with our strategy to continue to improve our customer churn rates, and relates to additional expenses incurred for our customer renewal team and our call center and support operations.

Software Development and Technical Support

Our software development and technical support staff have three essential responsibilities for which the accounting treatment varies depending upon the work performed: (i) costs associated with internal software development efforts are typically capitalized as software product costs and amortized over the estimated useful lives of the product; (ii) professional services performed for customers related to software customization projects are classified as cost of revenue; and (iii) all other activities are considered operating expenses and included within the software development and technical support operating expense category.

The table below summarizes our internal software development and technical support spending:

	Three months ended January 31		Percent	Six months ended January 31		Percent
	2013	2012	Change	2013	2012	Change
Total software development and technical support costs	$ 1,657	$ 1,317	25.8 %	$ 3,075	$ 2,582	19.1 %
Less: amount capitalized as software development	(420)	(439)	(4.3) %	(813)	(932)	(12.8)%
Less: direct labor classified as cost of revenues	(565)	(388)	45.6 %	(1,013)	(772)	31.2 %
Net software development and technical support costs classified as operating expenses	$ 672	$ 490	37.1 %	$ 1,249	$ 878	42.3 %

The Company increased total software development and technical support costs by 25.8% or $340,000 for the three months ended January 31, 2013, and by 19.1% or $493,000 for the six months ended January 31, 2013, compared to the same periods last year. Excluding expenses related to 50 Below and Ready2Ride, software development and technical support costs increased 14.4% and 10.9% for the three and six months ended January 31, 2013, respectively.

During the second quarter of fiscal 2013, the Company capitalized $420,000 of software development labor and overhead, versus $439,000 for the same period last year. Year to date through January 31, 2013, we capitalized $813,000, versus

$932,000 for the same period last year. The amount of software development costs capitalized will fluctuate from period to period based on the amount of time spent by our internal product management and development staffs on capitalizable activities, as defined by GAAP. The decline in fiscal 2013 relates to ongoing integration activities from our two most recent acquisitions, as time spent on these activities is not capitalized. Generally, we expect the amount of software development costs capitalized to increase as the business grows, which is consistent with our strategy to release new products, create enhancements to existing products, offer expanded data content and deliver superior services and technical support to our customers.

General and Administrative

General and administrative expenses primarily consist of personnel and related costs for executive, finance, human resources and administrative personnel, legal and other professional fees and other corporate expenses and overhead. General and administrative costs increased $880,000 or 88.6% for the three months ended January 31, 2013, compared to the same period last year, and increased $1,291,000 or 55.5% for the six months ended January 31, 2013, compared to the prior year period. This increase primarily relates to the acquisitions of 50 Below and Ready2Ride. Excluding expenses attributable to the 50 Below and Ready2Ride businesses, a large portion of which are acquisition-related legal and professional fees, general and administrative expenses declined 5.4% for the three months ended January 31, 2013 and increased 6.3% for the six months ended January 31, 2013, compared with the same periods in the prior year.

Depreciation and Amortization

Depreciation and amortization expenses consist of depreciation on fixed assets, which are composed of leasehold improvements and information technology assets, and the amortization of acquisition-related intangible assets. Costs associated with the amortization of software assets are a component of cost of revenue. Depreciation and amortization expense decreased $65,000 and $188,000 for the three and six months ended January 31, 2013, compared to the same periods last year as intangible assets related to an earlier acquisition have become fully amortized and older technology related to our infrastructure is getting replaced by newer cloud-based technology which is classified in general and administrative expense.

Interest Expense

Interest expense for the three months ended January 31, 2013 was $269,000, compared with $59,000 last year, and for the six months ended January 31, 2013, interest expense was $337,000, versus $121,000 last year. The increase in interest expense is consistent with the additional debt incurred in fiscal 2013 to fund the acquisitions of 50 Below and Ready2Ride. Interest expense also includes the amortization of the imputed discount related to the estimated Ready2Ride contingent earn-out liability.

Other Income (Expense)

Other income (expense) consists of foreign currency exchange rate gains and losses, interest income and other gains or losses.

Income Taxes

The Company has net deferred tax assets of $5,895,000, primarily consisting of net operating loss carryforwards and temporary book to tax differences. Income tax expense is provided for at the applicable statutory tax rate applied to current U.S. income before taxes, plus or minus any adjustments to the deferred tax assets and to the estimated valuation allowance against deferred tax assets. This does not represent a current cash obligation, as we continue to have net operating loss carryforwards to offset taxable income.

We recorded an income tax benefit of $835,000 and $709,000 for the three and six months ended January 31, 2013, compared to income tax expense of $61,000 and $229,000 for the same periods last year. In fiscal 2013, we recognized a tax gain of $941,000 for a change in our estimated valuation allowance due to the estimated increase in future taxable income related to the growth in our business and operational synergies as a result of the two acquisitions in fiscal 2013. In addition, there was a change in net deferred tax assets due to permanent differences for a true up related to incentive stock option expense and losses related to the Netherlands operation.

In fiscal 2012 we recognized a tax gain of $21,000 for a change in our estimated valuation allowance due to improved earnings. Income tax expense may vary from period to period as we continue to evaluate the valuation allowance against net deferred tax assets on a semi-annual basis.

Fiscal 2013 Rest of Year and Fiscal 2014 Outlook

As previously discussed, the remainder of fiscal 2013 and the first half of fiscal 2014 will be heavily affected by the closing and integration of our two fiscal 2013 acquisitions. The discussion below is intended to provide certain facts and historical information that would allow a reader to make an independent determination of ARI's results of operations for the remainder of fiscal 2013 and fiscal 2014.

Revenues

As previously discussed, ARI's business is primarily comprised of eCatalog and website solutions. The eCatalog category includes all of our electronic catalog products including both in-store and eCommerce offerings. This category also includes revenues from AccessorySmartTM, our newly launched aftermarket accessory product that we expect to aggressively grow over the next few years. The eCatalog business accounted for $13.6 million of total revenue, a 4.0% growth rate over the twelve months ended January 31, 2012. Our eCatalog business has historically grown at low single digit growth rates. As our new AccessorySmartTM product gains traction in the market, we expect our eCatalog organic growth rate to increase. We expect the gross margins of the eCatalog business to be in line with our historically reported numbers.

ARI's website business provides website hosting and maintenance to more than 5,500 dealers in the outdoor power, powersports, automotive wheel and tire aftermarket, marine & RV, medical equipment, and pool & spa industries. For the trailing twelve months ended October 31, 2012 and prior to the 50 Below acquisition, this segment generated revenue of $5.8 million, or 25% of ARI's total revenues, which represented annual growth of 12.5% over the prior twelve month period.

The retail division of 50 Below generated revenues of $8.8 million and $7.8 million for the fiscal years ended July 31, 2012 and 2011, respectively, and generated approximately $4.9 million in revenue for the six months ended January 31, 2013 (note, however, that only $1.7 million of these revenues are reflected in ARI's results, which represent the two months since the date of acquisition). This represents growth rates of 12.0% in fiscal 2012 and 11.0% for the six months ended January 31, 2013.

On a combined basis, we anticipate continued double-digit annual revenue growth rates on our website business. Additionally, we expect the gross margins on the website business to trend upward as we consolidate web platforms.

Our remaining businesses include lead generation, lead management, and professional services fees for custom projects. During the six months ended January 31, 2013, these businesses generated revenues of approximately $1.9 million, representing 14% of total revenues, many of which are non-recurring in nature. We expect revenues from these other businesses to decline over time, both in terms of absolute dollars and percentage of total revenue, as we continue to focus on our eCatalog and website businesses and rolling out new recurring revenue products.

EBITDA

Management believes EBITDA is helpful in understanding period-over-period operating results separate and apart from non-operating expenses and expenses pertaining to prior period investing activities, particularly given the Company's significant investments in capitalized software and its continuing efforts in completing acquisitions, which typically result in significant depreciation and amortization expense in subsequent periods. The Company uses EBITDA as a factor in evaluating potential acquisition targets and analyzing the pro forma impact of the acquisition on the Company. However, EBITDA has significant limitations as an analytical tool and should only be used cautiously in addition to, and never as a substitute for, operating income, cash flows or other measures of financial performance prepared in accordance with generally accepted accounting principles and may not necessarily be comparable to similarly titled measures of other companies.

The following table is a reconciliation of EBITDA for the periods indicated (in thousands):

	Six months ended January 31		Twelve months ended July 31	
	2013	2012	2012	2011
Net income	$ 117	$ 333	$ 1,055	$ 2,443
Interest	337	121	235	790
Amortization included in cost of sales	860	685	1,420	1,127
Depreciation and amortization	619	807	1,414	1,688
Income taxes	(709)	229	227	(1,017)
EBITDA	$ 1,224	$ 2,175	$ 4,351	$ 5,031
Revenue	$ 13,420	$ 10,911	$ 22,494	$ 21,334
EBITDA as a % of revenue	9.1 %	19.9 %	19.3 %	23.6 %

EBITDA as a percentage of revenues was 23.6% and 19.3% for the fiscal years ended July 31, 2011 and 2012, respectively. The fiscal 2012 decline resulted from strategic investments in investor relations, customer retention and satisfaction, and an enterprise-wide CRM system, a portion of which were one-time costs. The results of operations attributable to the acquired 50 Below and Ready2Ride businesses will not be accretive to EBITDA in fiscal 2013, but we do expect the acquisitions to be accretive in fiscal 2014, much like our results in fiscal 2010 and 2011 following our acquisition of Channel Blade Technologies in April 2009.

In the two years leading up to the Channel Blade acquisition, Channel Blade recorded operating losses of $2.5 and $0.9 million. We acquired Channel Blade in April 2009, toward the end of our 2009 fiscal year. We spent most of fiscal 2010 integrating the Channel Blade operations. In fiscal 2011, the first year of a fully integrated operation, ARI achieved record EBITDA. The recent 50 Below acquisition is similar in many respects to the Channel Blade acquisition of 2009. In the two years leading up to the acquisition, 50 Below recorded significant operating losses, as reflected in our current report on Form 8-K/A filed in February 2013. We anticipate the integration of 50 Below to take approximately one year; and while the operating results attributable to the 50 Below acquisition will not be accretive to EBITDA in fiscal 2013, we do anticipate that it will be accretive to EBITDA in fiscal 2014 while we conclude the majority of integration efforts. We further expect to substantially conclude the 50 Below integration efforts in fiscal 2014 and anticipate a return to EBITDA as a percentage of revenues in line with historical rates in fiscal 2015.

Liquidity and Capital Resources

The following table sets forth, for the periods indicated, certain cash flow information derived from the Company's financial statements:

`	Three months ended January 31		Percent	Six months ended January 31		Percent
	2013	2012	Change	2013	2012	Change
Net cash provided by operating activities	$ 868	$ 540	60.7 %	$ 1,377	$ 1,375	0.1 %
Net cash used in investing activities	(1,103)	(424)	(160.1)%	(3,629)	(962)	(277.2)%
Net cash provided by (used in) financing activities	172	(282)	161.0 %	1,104	(720)	253.3 %
Effect of foreign currency exchange rate changes on cash	(8)	9	(188.9)%	(12)	14	(185.7)%
Net change in cash	$ (71)	$ (157)	54.8 %	$ (1,160)	$ (293)	(295.9)%
Cash at end of period	$ 190	$ 841	(77.4) %	$ 190	$ 841	(77.4) %

Net cash provided by operating activities for the three months ended January 31, 2013 was $868,000, compared with $540,000 the year before. For the six months ended January 31, 2013, operating cash flows were $1,377,000, versus $1,375,000 the year before. A significant portion of this increase relates to operating cash flow conservation activities implemented in order to allow the Company to fund the acquisition of 50 Below. These cash conservation activities include paying management

bonuses in stock rather than cash, managing the timing of trade vendor payments, and reducing the amount of discretionary spend items such as travel and entertainment. These actions were necessary in order to fund the acquisition of 50 Below during the quarter. ARI's cash flows have historically reflected moderate seasonality, with the fiscal second quarter being the quarter in which the least amount of cash flows are generated. The third and fourth fiscal quarters have historically generated the highest percentage of cash flows.

Cash used in investing activities was $1,103,000 and $3,629,000 for the three and six months ended January 31, 2013, respectively. Year to date, ARI paid cash of $2,478,000 for the acquisitions of Ready2Ride and 50 Below, capitalized $818,000 of software development costs, and acquired technology equipment of $435,000. We will continue to invest cash in the business for the development of new products and upgrades to existing products.

The Company had net cash provided by financing activities of $172,000 and $1,104,000 for the three and six months ended January 31, 2013, respectively, compared to net cash used in financing activities of $282,000 and $720,000 for the same periods last year. The Company borrowed an additional $1,000,000 of debt from Fifth Third to fund its acquisition of Ready2Ride in August 2012 and borrowed an additional $3,5000,000 for its acquisition of 50 below in November 2012. Terms and conditions of the notes are detailed in the footnotes to the financial statements.

On March 8, 2013 our Credit Facilities were amended to waive the provisions of the Agreement that would prohibit ARI from issuing additional shares of common stock of the Company and specify how the proceeds raised from an issuance of capital securities would be used. Under the amendment, Fifth Third consented to the issuance of equity securities by the Company and specified that the first $1.5 million received by the Company from the issuance of securities would be applied against the outstanding balance of the Senior Secured Term Note with Fifth Third. Additionally, the amendment revised the required fixed charge coverage ratio as follows: 0.90x for the four fiscal quarter period ended January 31, 2013; 1.00x for the four fiscal quarter period ending April 30, 2013, 1.15x for the four fiscal quarter period ending July 31, 2013; and 1.20x thereafter. See Part II, Item 5 – Other Information for additional information about the amendment to the Loan and Security Agreement with Fifth Third.

Management believes that current cash balances and its ability to generate cash from operations, as well as the existing availability under our line of credit with Fifth Third, are sufficient to fund our operating needs over the next twelve months. Under the terms of the Senior Secured Term Note with Fifth Third, all outstanding principal and accrued interest becomes due and payable as of December 15, 2013. The Company expects to either amend or refinance our existing Credit Facilities prior to December 15, 2013; although there can be no assurance that this will occur.

Off-Balance Sheet Arrangements

The Company has no significant off-balance sheet arrangements that have or are reasonably likely to have a current or future effect on its financial condition, revenue or expenses, results of operations, liquidity, capital expenditures or capital resources.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

Not Applicable.

Item 4. Controls and Procedures

The Company has established disclosure controls and procedures to ensure that material information relating to it, including its consolidated subsidiaries, is made known on a timely basis to the officers who certify our financial reports and to other members of senior management and the Board of Directors.

The Company's management, with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this report. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of such date, the Company's disclosure controls and procedures are effective (1) in recording, processing, summarizing and reporting, on a timely basis, information required to be disclosed by the Company in the reports that it files or submits under the Exchange Act and (2) to ensure that information required to be disclosed in the reports it files or submits under the Exchange Act is accumulated and communicated to its management, including the Chief Executive Officer and Chief Financial Officer, to allow timely decisions regarding required disclosure.

There have not been any changes in our internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) that occurred during the quarter ended January 31, 2013 that have materially affected, or are reasonably likely to materially affect the Company's internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings

From time to time, the Company may be involved in litigation relating to claims arising out of its operations in the usual course of business. No material legal proceedings to which the Company is a party arose during the three months ended January 31, 2013.

Item 1A. Risk Factors

The following discussion is intended to supplement the other risks and uncertainties described in full detail in Item 1A of the Company's annual report on Form 10-K for the fiscal year ended July 31, 2012. This discussion should be read in conjunction with and in addition to the risk factors described in the Form 10-K, and is not intended to replace or supersede any of those risk factors.

We may not be able to identify, acquire and successfully integrate acquisitions, including the recently acquired 50 Below retail division and Ready2Ride businesses.

A key component of our growth strategy has been and will continue to be acquisitions and other business development opportunities that solidify or accelerate our market position in our core offerings and vertical markets. The successful implementation of this strategy depends upon our ability to identify suitable acquisition candidates, acquire such businesses on acceptable terms, finance the acquisition and integrate their operations successfully into ARI. There can be no assurance that such candidates will be available or, if such candidates are available, that the price will be attractive or that we will be able to identify, acquire, finance or integrate such businesses successfully. In addition, in pursuing such acquisition opportunities, we may compete with other entities with similar growth strategies; these competitors may be larger and have greater financial and other resources than ARI. Competition for these acquisition targets could also result in increased prices of acquisition targets and/or a diminished pool of companies available for acquisition.

The successful integration of these acquisitions also may involve a number of additional risks, including: (i) the inability to retain the clients of the acquired business; (ii) the lingering effects of poor client relations or service performance by the acquired business, which also may taint our existing business; (iii) the inability to retain the desirable management, key personnel and other employees of the acquired business; (iv) the inability to fully realize the desired efficiencies and economies of scale; (v) the inability to establish, implement or monitor ARI's existing standards, controls, procedures and policies on the acquired business; (vi) diversion of management attention; and (vii) exposure to client, employee and other legal claims for activities of the acquired business prior to acquisition. In addition, any acquired business could perform significantly worse than expected.

As described in this report, ARI recently acquired two new businesses: the retail division of 50 Below, which was acquired in a transaction pursuant to Sections 363 and 365 of the United States Bankruptcy Code in November 2012, and Ready2Ride, which we acquired in October 2012. We consider the successful integration and performance of these businesses to be material to the future success of ARI as a whole. The integration and future performance of these businesses are subject to the significant risks and uncertainties described above, and there can be no assurance that we will be able to successfully integrate these businesses to the extent and in the timeframes that we currently anticipate, or that their financial performance will ultimately meet our current expectations.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds

None.

Item 3. Defaults upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

On March 8, 2013, the Company entered into the Third Amendment to the Loan and Security Agreement (as amended, the "Loan and Security Agreement").

Under the Loan Agreement Amendment, the Loan and Security Agreement was amended primarily for the following purposes: (i) to permits an additional add-back to EBITDA ("Adjusted EBITDA") for non-cash expenses limited to bonuses and board director fees paid in shares of the Company's common stock, provided that any conversion of non-cash expenses into cash payments will be permitted only with the prior written of Fifth Third; (ii) to amend the definition of EBITDA to permit additional add-backs for certain transaction expenses; (iii) to amend the fixed charge coverage ratio to be calculated based on Adjusted EBITDA, rather than EBITDA and to exclude certain extraordinary gains; (iv) to amend the required fixed charge coverage ratio for the four fiscal quarter periods ending January 31, 2013 and April 30, 2013 to 0.90x and 1.00x, respectively; (v) to require delivery of the personal financial statement of Roy W. Olivier within 120 days after the end of each calendar year; (vi) to restrict the Company's ability to enter into certain transactions without the prior written consent of Fifth Third, including, without limitation, certain change in control transactions, reclassifications, reorganizations and recapitalizations of the Company's Common Stock or any compulsory share exchange pursuant to which any of the Company's common stock is effectively converted into and exchanged for other securities, cash or property; and (vii) to permit the Company to use the net cash proceeds from an equity raise transaction (as described below) in excess of $1,500,000 for working capital or to prepay the outstanding principal balance under the Sifen Note.

The Loan Agreement Amendment also contains Fifth Third Bank's consent to the Company raising additional capital by selling and issuing additional equity securities, and waivers by Fifth Third of the provisions of the Loan and Security Agreement that would otherwise have prohibited such a transaction, subject to certain terms and conditions. Such terms and conditions include, among others, a deemed event of default under the Loan and Security Agreement in the event the Company does not raise at least $250,000 in net cash proceeds on or before May 15, 2013 or any portion of the first $1,500,000 of such net cash proceeds is not used to prepay the outstanding principal balance of the Term Loan (the "Mandatory Prepayment"); and payment of a nonrefundable fee of $100,000 in the event the Company does not raise at least $1,500,000 on or before May 15, 2013 or any portion of the such amount is not used to make the Mandatory Prepayment. The Loan Agreement Amendment also contains other terms and conditions customary for an agreement of this nature. The Company was required to pay a $30,000 amendment fee to Fifth Third Bank in connection with the Loan Agreement Amendment.

Item 6. Exhibits

2.1 Bill of Sale dated as of November 28, 2012, incorporated by reference to Exhibit 2.1 to the Company's Current Report on Form 8-K filed on December 4, 2012.

2.2 Assumption and Assignment and Transition Services Agreement dated as of November 28, 2012, incorporated by reference to Exhibit 2.2 to the Company's Current Report on Form 8-K filed on December 4, 2012.

4.1 Secured Non-Negotiable Subordinated Promissory Note dated November 28, 2012 issued to Michael D. Sifen, Inc., incorporated by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K filed on December 4, 2012.

10.1 Second Amendment to Loan and Security Agreement and Other Loan Documents, dated as of November 28, 2012, by and between ARI Network Services, Inc. and Fifth Third Bank, incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 4, 2012.

10.2 Second Amendment to Rights Agreement, dated as of November 28, 2012, between ARI Network Services, Inc. and American Stock Transfer & Trust Company, LLC, incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 4, 2012.

31.1 Rule 13a-14(a)/15d-14(a) Certification of Chief Executive Officer.

31.2 Rule 13a-14(a)/15d-14(a) Certification of Chief Financial Officer.

32.1 Section 1350 Certification of Chief Executive Officer.

32.2 Section 1350 Certification of Chief Financial Officer.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on this 12th day of March, 2013.

ARI NETWORK SERVICES, INC.

(Registrant)

By:/s/ Roy W. Olivier_

Roy W. Olivier

President and Chief Executive Officer

By:/s/ Darin R. Janecek_

Darin R. Janecek

Vice President of Finance and Chief Financial Officer