Epizyme, Inc.
Form 424B5
March 18, 2015
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As Filed Pursuant to Rule 424(b)(5)
Registration No. 333-196692

Prospectus Supplement

(To Prospectus Dated June 27, 2014)

6,000,000 Shares

Epizyme, Inc.

Common Stock

$20.75 Per Share

We are offering 6,000,000 shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol EPZM. The last reported sale price of our common stock on The NASDAQ Global Market on March 17, 2015 was $21.13 per share.

Investing in our common stock involves risks. See Risk Factors beginning on page S-19.

We are an emerging growth company under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements. See Prospectus Supplement Summary Implications of Being an Emerging Growth Company.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	$ 20.75	$ 124,500,000
Underwriting discount(1)	$ 1.245	$ 7,470,000
Proceeds, before expenses, to Epizyme, Inc.	$ 19.505	$ 117,030,000

(1) We refer you to Underwriting beginning on page S-59 of this prospectus supplement for additional information regarding total underwriter compensation.

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to 900,000 additional shares of our common stock. See Underwriting for more information.

The underwriters expect to deliver the shares to purchasers on or about March 23, 2015 through the book-entry facilities of The Depository Trust Company.

Joint Book-Running Managers

Leerink Partners | **Cowen and Company** *Lead Manager* | **RBC Capital Markets**

JMP Securities

Co-Managers

SunTrust Robinson Humphrey | **Mizuho Securities**

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PROSPECTUS SUPPLEMENT

PROSPECTUS

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where You Can Find More Information and Incorporation of Certain Information by Reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise stated, all references in this prospectus supplement and the accompanying prospectus to we, us, our, Epizyme, the Company and similar designations refer, collectively, to Epizyme, Inc., a Delaware corporation, and its

consolidated subsidiary.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predic target, potential, will, would, could, should, continue, and similar expressions are intended to identify forw statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement include, among other things, statements about:

- our plans to develop and commercialize novel epigenetic therapies for cancer patients;
- our ongoing and planned clinical trials, including the timing of initiation of 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 portfolio;
- our expectations related to the use of proceeds for this offering; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus supplement, particularly in the Risk Factors section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors beginning on page S-19 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

Company Overview

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for cancer patients. We have built a proprietary product platform that we use to create small molecule inhibitors of a 96-member class of enzymes known as histone methyltransferases, or HMTs. HMTs are part of the system of gene regulation, referred to as epigenetics, that controls gene expression. Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. These altered HMTs are referred to as oncogenes. The HMT target class has many potential oncogenes and, we believe, presents the opportunity to create, develop and commercialize multiple epigenetic therapeutics.

Our lead product candidate, EPZ-6438, is an inhibitor that targets the EZH2 HMT. We are currently conducting a Phase 1/2 clinical trial of EPZ-6438 in patients with relapsed or refractory B-cell lymphoma or advanced solid tumors. In 2014, we and our collaboration partner Eisai Co. Ltd., or Eisai, completed enrollment in the dose escalation portion of this Phase 1/2 clinical trial and disclosed the first clinical responses to treatment with EPZ-6438 from this ongoing Phase 1/2 clinical trial. These clinical responses were observed in heavily pretreated and relapsed or refractory patients with non-Hodgkin lymphoma, including of both germinal center and non-germinal center cells-of-origin, and in a patient with an INI1-deficient tumor. In March 2015, we reacquired global rights to develop, manufacture and commercialize EPZ-6438 outside of Japan from Eisai. As we begin the process of transitioning the ongoing development and manufacturing activities of EPZ-6438 to us, we are continuing to dose patients under both the dose escalation and dose expansion portions of the Phase 1/2 study and plan to commence a five-arm Phase 2 portion of the Phase 1/2 trial in Europe in the second quarter of 2015. We expect to enroll approximately 150 patients in this trial in both relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma patients, prospectively stratified by cell of origin and EZH2 mutational status. We also plan to commence a Phase 2 trial in adult patients with INI1-deficient tumors and a Phase 1 trial in pediatric patients with INI1-deficient tumors in the second half of 2015.

Our therapeutic strategy is to treat the underlying causes of specific cancers by blocking the misregulated activity of oncogenic HMTs. HMTs regulate gene expression by adding marks, called methyl groups, to specific locations on the proteins of human chromosomes, or histones, a process known as methylation. Oncogenic HMTs inappropriately mark these locations. As a result, the gene expression necessary for healthy, normally functioning cells is altered, thereby causing disease. Oncogenic HMTs drive multiple types of cancer, including hematological cancers and solid tumors.

In 2011, our scientists defined the 96-member HMT target class, which is referred to as the HMTome. Previously, specific HMTs were known, but a comprehensive identification of the entire target class did not exist. We subsequently analyzed cancer genome databases to enable us to prioritize these HMTs for our drug discovery activities based on the potential oncogenic role of these HMTs, the clinical need of patients with the relevant cancers and the possible clinical development and regulatory pathway for related inhibitors. The clinical development plan for each of our therapeutic product candidates is directed towards targeted cancer patient

populations. Because we are tailoring our epigenetic therapeutics for discrete, identifiable patient populations with specific cancers, we believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions.

We currently have two HMT inhibitors in clinical development for the treatment of patients with certain cancers and believe we are the first company to conduct clinical trials of HMT inhibitors and demonstrate objective responses in patients in such a trial. In 2012 we initiated a Phase 1 clinical trial of EPZ-5676, an inhibitor targeting the DOT1L HMT and our second most advanced product candidate, in adult patients with MLL-r, an acute leukemia with genetic alterations of the *MLL* gene. In 2013, we completed enrollment in the dose escalation portion of this Phase 1 clinical trial and, in 2014, we completed enrollment in a 90 mg/m^2/day expansion cohort and disclosed the first clinical responses to treatment with EPZ-5676 in heavily pretreated and relapsed or refractory patients with MLL-r. We are currently enrolling up to an additional 20 MLL-r patients in an expansion cohort to investigate the activity of EPZ-5676 at a dose of 54 mg/m^2/day. We are also conducting a Phase 1 clinical trial of EPZ-5676 in pediatric patients with MLL-r, which we initiated in 2014.

In 2015, we plan to execute on the following clinical plans:

- Continue dosing patients who remain on study in the dose escalation portion of our ongoing Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma;

- Continue dosing patients in two fully enrolled six-patient expansion cohorts in our ongoing Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma, with one cohort at 800 mg and one cohort at 1600 mg;

- Initiate the Phase 2 portion of our Phase 1/2 clinical trial of EPZ-6438 in Europe in adult non-Hodgkin B-cell lymphoma patients in which patients will be prospectively stratified based on cell of origin and EZH2 mutational status into one of five arms;

- Initiate a Phase 2 clinical trial of EPZ-6438 in adult patients with INI1-deficient tumors such as synovial sarcoma;

- Initiate a Phase 1 clinical trial of EPZ-6438 in pediatric patients with INI1-deficient tumors such as malignant rhabdoid tumors, or MRT;

- Initiate standard clinical pharmacology studies of EPZ-6438;

- Complete enrollment in a 20 patient expansion cohort in our ongoing Phase 1 clinical trial of EPZ-5676 in adult MLL-r patients at 54 mg/m^2/day; and

Complete enrollment in the ongoing Phase 1 clinical trial of EPZ-5676 in pediatric MLL-r patients.

In addition to our clinical programs, we also have a pipeline of HMT inhibitors in preclinical development that target our other prioritized HMTs in the HMTome. These programs are directed to specific cancers, including both hematological and solid tumors. Three of these HMT programs, including our compounds directed to the PRMT5 HMT, are currently partnered with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK.

If we see evidence of a therapeutic effect in any of our programs, we intend to meet with regulatory authorities to discuss the possibility of an expedited clinical development and regulatory pathway for the applicable program. If eligible, we intend to apply for expedited review and approval programs from the United States Food and Drug Administration, or FDA, including breakthrough therapy and fast track designations.

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 EPZ-6438.

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Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our EZH2 program, including EPZ-6438, 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 amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization outside of Japan of EPZ-6438 and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture EPZ-6438 and any other EZH2 product candidates in Japan. In connection with the amended and restated agreement, we agreed to pay Eisai an upfront payment of $40.0 million, specified milestone payments based on our development and commercialization of EZH2 products outside of Japan and royalties on net sales of EZH2 products outside of Japan.

In addition to our collaborations with Eisai and GSK, we are also a party to a collaboration agreement with Celgene. These collaborations have provided us with $188.7 million in non-equity funding through December 31, 2014. Our collaborations with Celgene and GSK also provide us with the potential for significant research, development, regulatory and sales-based milestone payments, as well as royalties on any net product sales. Our key therapeutic collaborations are as follows:

- A collaboration with Celgene under which we have granted Celgene a license outside of the United States to our DOT1L program, which includes EPZ-5676, and the option during a defined period that expires in July 2015 to license other HMT programs outside of the United States. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment. We retain all United States development and commercialization rights for our DOT1L program and any other programs that we license to Celgene under this collaboration.

- A collaboration with GSK under which we have granted GSK a worldwide license to three specified HMT targets, including the PRMT5 HMT. Potential inhibitors of these targets are currently in preclinical development with GSK.

- An amended and restated collaboration with Eisai, under which we have granted Eisai a license to our EZH2 program in Japan, including EPZ-6438. We have retained worldwide development, manufacturing and commercialization rights, excluding Japan. 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.

We have also entered into an agreement with Roche Molecular Systems, Inc., or Roche, for the development of a companion diagnostic for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations.

Strategy

Our goal is to be a leader in the discovery, development and commercialization of novel epigenetic therapies for cancer patients. We systematically identify the genetic alterations that create oncogenes, select patients in whom the identified genetic alteration is found and then design small molecule therapies to inhibit the oncogenic activity. Our approach is part of a broader trend towards personalized therapeutics based on first identifying the underlying cause of a disease afflicting specific patient populations, applying rational drug design tools to create a therapeutic to inhibit a molecular target in the identified disease pathway and using diagnostic methods to select the right patients for treatment. Because we are tailoring our therapeutics for targeted cancer patient populations, we believe that many of

our products may qualify for orphan drug designation in the United States, the European Union and other regions and have been granted orphan drug designation in the United States and the European Union for EPZ-5676.

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Key elements of our strategy to achieve our goal are to:

Rapidly Advance the Clinical Development of Our Two Lead Product Candidates. We are conducting a Phase 1/2 clinical trial of EPZ-6438 for the treatment of non-Hodgkin lymphoma and advanced solid tumors including INI1-deficient tumors, such as synovial sarcoma and malignant rhabdoid tumors and plan to initiate the Phase 2 portion of the Phase 1/2 trial in patients with non-Hodgkin lymphoma in Europe in the second quarter of 2015, as well as a Phase 1 trial in pediatric patients with INI1-deficient tumors in the second half of 2015 and a Phase 2 trial in adult patients with INI1-deficient tumors in the second half of 2015. We are also conducting two Phase 1 clinical trials of EPZ-5676 for the treatment of MLL-r in both adult and pediatric patients. If we see compelling early 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. This approach is similar to the clinical development pathway that was used by the sponsor of the cancer therapeutic Zelboraf® which was included by the FDA in its 2011 report on Innovative Drug Approvals and which received marketing approval from the FDA within five years of initiating Phase 1 clinical trials. If safe and sufficiently active in the target patient populations, we believe that our two lead product candidates may be able to rely on an expedited regulatory approval process because these product candidates have the potential to satisfy the requirements that applied to other targeted cancer therapeutics as well as the FDA s new breakthrough therapy designation, such as treating a life-threatening disease and providing a major advance in treatment. We cannot predict whether or when any of our product candidates will prove effective or safe in humans, if they will receive regulatory approval or if we will be able to participate in FDA expedited review and approval programs, including breakthrough and fast track designation.

Pursue Expansion Indications for our Two Lead Product Candidates. We apply our proprietary product platform to identify additional cancers that may be treated with each of our product candidates beyond the initial indication of interest. For instance, INI1-deficient tumors are a potential expansion indication for EPZ-6438 that we identified internally. We are also continuing to look at other genetic alterations affecting EZH2, and its role in oncogenesis in a range of other hematological malignancies and solid tumors.

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 in our GSK collaboration. We plan to seek to retain similar rights 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.

Use Our Product Platform to Build a Pipeline of Proprietary HMT Inhibitors. There are 96 HMT enzymes in the HMTome. We regularly prioritize these HMTs based on their potential as attractive targets for personalized therapeutics. We are using our intellectual property, expertise and knowledge to create small molecule inhibitors of the HMT targets that we have prioritized. To date, we have invented novel, potent small molecule inhibitors for 17 HMTs. We intend to advance certain of these inhibitors into clinical trials.

Leverage Collaborations. We have established therapeutic collaborations with Celgene, GSK and Eisai for our most advanced HMT programs. These collaborations provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our 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.

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Develop Companion Diagnostics for Use with Our Therapeutic Product Candidates. For many of our therapeutic product candidates, we may seek to develop a companion diagnostic for the identification of patients with the cancers that we seek to treat with our therapeutic product candidates. 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 will 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 to develop a companion diagnostic, based on currently available technology, for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations and are relying on existing laboratory tests for use with EPZ-5676 to identify MLL-r patients.

The Epizyme Approach

We are discovering and developing HMT inhibitors as novel epigenetic therapeutics for cancer patients. We are applying our approach to the HMTome, with a focus on HMTs that we believe have the potential to be oncogenic, due to a variety of genetic alterations.

Background of Epigenetics. Epigenetics is a regulatory system that controls gene expression without altering the makeup of the genes themselves. Genes are composed of DNA. When properly read and translated, genes provide the blueprint for making individual proteins of the body. Epigenetic control of gene expression relies on a well-orchestrated collection of enzymes to perform precisely timed and located chemical reactions. When the function of these epigenetic enzymes is altered, the program of gene expression is changed in ways that often leads to disease.

Like thread wrapped around a spool, the DNA of chromosomes is packed into cell nuclei by wrapping around groups of proteins called histones, together forming packages of combined DNA and histone units known as nucleosomes. How tightly packed the nucleosomes are determines how easily individual genes on the DNA may be expressed. The tightness of the packing is controlled by the placement of small chemical groups acetyl groups, methyl groups and others onto specific sites in the DNA and the histone proteins by particular epigenetic enzymes. Where, when and how many of these small chemical groups are deposited determines which genes in a cell are turned on or off at any particular time.

Cancer and HMTs. The HMT class of enzymes 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.

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.

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The Epizyme Product Platform

When Epizyme was founded, we recognized that the HMT target class might contain many potential oncogenes and, therefore, presented the opportunity to create, develop and commercialize multiple epigenetic therapeutics. To realize this potential opportunity, we created and continue to expand and enhance our proprietary product platform. Our product platform includes intellectual property, know-how, expertise, proprietary biological information, biochemical assays, a library of novel HMT inhibitors and crystal structures of HMT enzymes bound with our small molecules. We have used, and continue to apply, our product platform to:

- define the HMTome;
- determine the roles of HMTs as oncogenes;
- identify potent and selective small molecule inhibitors of prioritized HMTs;
- optimize those small molecules as potential drug candidates; and
- develop companion diagnostics with our collaborators, where needed, for use with our therapeutic product candidates.

We invented EPZ-6438 and EPZ-5676, our two lead product candidates, and our pipeline of preclinical drug candidates using our proprietary product platform.

Define the HMTome. We defined the HMTome and published our findings in *Chemical Biology & Drug Design* in August 2011. The HMTome represents an unusually large target class, and therefore presents a broad opportunity to identify therapeutic applications.

Determine HMT Oncogenicity. After comprehensively defining the HMTome, we applied a rigorous analysis to prioritize HMTs for our drug discovery programs. Specifically:

- We generated hypotheses as to the oncogenic nature of particular HMTs based on our proprietary experimental data as well as public databases, such as The Cancer Genome Atlas, a project to catalogue genetic mutations responsible for cancer supervised by the National Cancer Institute and the National Human Genome Research Institute. We published our findings regarding our hypotheses as to the oncogenic nature of particular HMTs in *Oncogene* in February 2013.
- We designed and created proprietary *in vitro* biochemical and cellular assays to confirm the enzymatic function and oncogenic mechanism of various HMTs. For example, using these assays, we discovered the oncogenic role in a genetically defined subtype of non-Hodgkin lymphoma played by a point mutation in EZH2. A point mutation is a type of genetic alteration in which a single nucleotide base in a gene is

substituted, added or deleted. This discovery formed the basis of our program in which we identified EPZ-6438. Our research on the EZH2 point mutation was published in the *Proceedings of the National Academy of Sciences* in December 2010.

Similarly, in *in vitro* preclinical studies conducted by us, EPZ-6438 induced apoptotic cell death and, in preclinical animal models conducted by us, EPZ-6438 caused dose-dependent regression of malignant rhabdoid tumors and prevention of tumor regrowth after dosing cessation. Our research on tumor regressions in genetically altered malignant rhabdoid tumors by inhibition of EZH2 was published in the *Proceedings of the National Academy of Sciences* in April 2013.

We identified the patient populations with the oncogenic HMTs to determine that we were pursuing areas of significant unmet medical need.

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Identify Potent and Selective Small Molecule Inhibitors. We then screened for potent and selective inhibitors that have the potential to be novel, safe and effective pharmaceuticals. Specifically:

- We have designed and built proprietary biochemical assays that we use to screen for potent and selective inhibitors of the prioritized HMTs. We refer to these assays together as our HMTome cross screen. Our HMTome cross screen includes our high priority HMTs. We have also included a number of other HMTs to determine whether the compounds that we screen inhibit the HMT of interest selectively.

- We have created more than 650 proprietary crystal structures of enzymes bound with HMT inhibitors. We use these structures to guide our efforts to select HMT inhibitors that we believe have the potential to be developed into safe and effective pharmaceuticals and to optimize these inhibitors through medicinal chemistry efforts.

Optimize Small Molecule Compounds. We have created a proprietary library of more than 29,000 compounds in 27 distinct chemical series. Within these 27 distinct series, there are examples of multiple modes of inhibition of HMTs, thereby increasing the likelihood of their binding to a target HMT in a manner that may have a pharmaceutical effect. We have further optimized many of these small molecule compounds to have drug-like properties, including the ability to be absorbed and maintained at blood levels necessary to treat cancers. Many of these compounds are highly selective for specific HMTs.

Develop Companion Diagnostics. One element of our approach to cancer treatment is to develop a companion diagnostic for use with each therapeutic product candidate we develop, unless we believe existing, available technology may be sufficient to identify the patients we seek to treat. We are working with a collaborator to develop one such companion diagnostic, applying our knowledge about the target HMT and using currently available diagnostic technologies to the extent possible in order to minimize development and regulatory risk of our diagnostic programs. We believe that this approach will help us to access the best technology for each program and control diagnostic development costs. We intend to use the companion diagnostic to identify and stratify patients for our clinical trials who have the target cancers that we are seeking to treat with our therapeutic product candidate. We believe that including these patients may increase the likelihood that we will see early evidence of a therapeutic effect in our trials.

We believe that our product platform provides us with an important competitive advantage in identifying oncogenic HMTs and creating novel epigenetic therapeutics to treat the cancers caused by these HMTs.

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Product Pipeline

The following table summarizes key information about our two most advanced product candidates:

Product Candidate	Clinical Populations	Stage of Development	Commercial Rights	Diagnostic Collaborator
EPZ-6438 (EZH2 inhibitor)	Non-Hodgkin lymphomas, including germinal center diffuse large B-cell lymphoma and follicular lymphoma as well as non-germinal center DLBCL, including primary mediastinal B-cell lymphoma (EZH2)	Phase 1/2 clinical trial ongoing Phase 1 dose escalation complete; Phase 1 dose expansion fully enrolled at the highest two tested dose levels Phase 2 trial for expanded population of non-Hodgkin lymphoma patients expected to initiate in the second quarter of 2015	Epizyme: Worldwide rights, ex-Japan Eisai: Japan	Roche (Non-Hodgkin lymphoma with EZH2 point mutations)
	Other solid tumors such as synovial sarcoma and MRT (INI1-deficient)	Phase 1 trial for pediatric patients with INI1-deficient tumors, including MRT, expected to initiate in the second half of 2015 Phase 2 trial for adult patients with INI1-deficient tumors, including synovial sarcoma, expected to initiate in the second half of 2015 Clinical pharmacology studies evaluating food effects and drug/drug interactions expected to initiate in 2015		None - existing standard of care immunohistochemical testing used at time of diagnosis to be utilized for studies in INI1-deficient tumors

EPZ-5676 (DOT1L inhibitor)	Acute leukemias with alterations in the *MLL* gene MLL-r subtype of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL, in adult patients (Chromosomal translocation involving the *MLL* gene) MLL-r in pediatric patients (Chromosomal translocation involving the *MLL* gene)	Phase 1 MLL-r adult patient trial ongoing Dose escalation fully enrolled in MLL-r adult patient trial MLL-r only adult expansion enrolling Phase 1 MLL-r pediatric patient trial enrolling	Epizyme: United States Celgene: Rest of world	None - existing standard of care molecular testing used at time of diagnosis to be utilized for studies in MLL-r leukemia

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In addition to the therapeutic programs listed above, we are working with GSK on three specified HMT inhibitors, including inhibitors directed to the PRMT5 HMT, that are in preclinical development and for which GSK holds commercial rights. We also have active drug discovery programs for other HMTs that we consider to be priority targets.

EPZ-6438 EZH2 Inhibitor

Overview. We are developing EPZ-6438 as an orally available small molecule inhibitor of EZH2 for the treatment of non-Hodgkin lymphoma patients and for the treatment of patients with INI1-deficient solid tumors, such as synovial sarcoma, a soft tissue sarcoma, and malignant rhabdoid tumor, a primarily pediatric cancer with high unmet medical need. In June 2013, Eisai and we initiated a Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma. In March 2015, we completed enrollment of two expansion cohorts of the Phase 1 dose escalation portion of the trial at clinical sites in France. In November 2014, we and Eisai released data from the Phase 1 dose escalation portion of the trial. In this portion of the trial, EPZ-6438 exhibited favorable safety and tolerability as well as monotherapy activity in non-Hodgkin lymphoma, including germinal center and non-germinal center B-cell lymphomas with wild-type EZH2, and INI1-deficient tumors. On the basis of these trial results, a recommended Phase 2 dose has been selected. We expect to initiate the Phase 2 portion of the trial in non-Hodgkin lymphoma patients in which patients will be prospectively stratified based on cell of origin and EZH2 mutational status in Europe in the second quarter of 2015 as well as a Phase 2 trial for the treatment of adults with INI1-deficient tumors, including synovial sarcoma, in the second half of 2015. These two Phase 2 trials are intended to provide an initial assessment of efficacy, or proof-of-concept, in two cancer types that we currently seek to treat with EPZ-6438. Additionally, in the second half of 2015, we plan to initiate a Phase 1 dose escalation study of EPZ-6438 in pediatric patients with INI1-deficient tumors, including MRT.

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 EPZ-6438. Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our EZH2 program, including EPZ-6438, 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 amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization, outside of Japan, of EPZ-6438 and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture EPZ-6438 and any other EZH2 product candidates in Japan. In connection with the amended and restated agreement, we agreed to pay Eisai an upfront payment of $40.0 million, specified milestone payments based on our development and commercialization of EZH2 products outside of Japan and royalties on net sales of EZH2 products outside of Japan.

Clinical Development. We are conducting our ongoing Phase 1/2 clinical trial of EPZ-6438 in two parts. The Phase 1 portion of this first-in-human clinical trial is an open label dose escalation trial. The Phase 2 portion will be conducted in two stages. All patients in the Phase 2 trial will be dosed at the recommended Phase 2 dose as determined in the Phase 1 clinical trial. If the pre-specified number of responses are observed in the first stage of the Phase 2 part of this clinical trial, enrollment will continue into the second stage. Both the Phase 1 and Phase 2 clinical trials provide for the assessment of the safety and tolerability and pharmacokinetics of EPZ-6438 and include various exploratory pharmacodynamics and translational research objectives.

The primary objective of the Phase 1 clinical trial is to evaluate the safety and tolerability of EPZ-6438 and to determine the recommended dose for Phase 2 trials.

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Secondary objectives of the Phase 1 clinical trial are to:

- explore the pharmacokinetic activity, including evaluating the fraction of orally administered drug that reaches systemic circulation, of EPZ-6438;
- explore the pharmacodynamic activity of EPZ-6438; and
- evaluate early evidence of anti-tumor activity in patients.

In the Phase 1 trial, EPZ-6438 is being administered orally as a monotherapy, twice daily in 28-day cycles in patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma. A total of 24 patients were enrolled in one of five dose cohorts at dose levels of 100, 200, 400, 800, or 1600 mg. This dose escalation portion of the trial allowed for, but did not require, the enrollment of patients with non-Hodgkin lymphoma and INI1-deficient tumors. Of the 24 enrolled patients, 12 patients had a diagnosis of non-Hodgkin lymphoma and 12 patients had advanced solid tumors, two of which were INI1-deficient. This patient population was heavily pre-treated, with 14 patients having received between two and four prior therapies and nine having received more than four prior therapies. As of an October 2014 data cut-off, 10 of the non-Hodgkin lymphoma patients and two of the INI1-deficient patients were evaluable for efficacy. Four of the 10 non-Hodgkin lymphoma patients evaluable for efficacy achieved a partial response or better, including one complete response, which remained ongoing at 14 months as of January 23, 2015, and one of the two evaluable INI1-deficient patients achieved a complete response, which remained ongoing at nearly nine months as of January 23, 2015. Four of the 10 non-Hodgkin lymphoma patients and one INI1-deficient patient from the dose escalation remain on study with treatment durations ranging from seven to 14 months as of January 23, 2015. Confirmatory sequencing in a central laboratory showed that all 10 non-Hodgkin lymphoma patients evaluable for efficacy had wild-type EZH2.

In the trial results to date, EPZ-6438 has exhibited a favorable safety and tolerability profile. Specifically, one dose-limiting toxicity at 1600 mg has been reported. This safety and tolerability profile suggest that combination with a range of other non-Hodgkin lymphoma therapies may be possible. We are currently evaluating a range of potential combinations preclinically.

Based on the Phase 1 dose escalation results, a recommended Phase 2 dose of 800 mg was selected. We have fully enrolled two ongoing six-patient expansion cohorts, one at 800 mg and one at 1600 mg. We plan to provide an update on data from the dose escalation portion of the study at a medical conference in mid-2015 and data from these expansion cohorts by the end of 2015.

Subject to our ongoing discussions with regulatory authorities, we expect to initiate the Phase 2 portion of this trial in non-Hodgkin B-cell lymphoma patients in the European Union in the second quarter of 2015. Our plan for this Phase 2 portion of the clinical trial provides for prospective stratification of patients based on cell of origin and EZH2 mutational status and will enroll five distinct patient populations in five clinical trial arms, allowing us to discretely assess EPZ-6438 in the following patient groups: germinal center DLBCL with wild-type EZH2, non-germinal center B-cell DLBCL, germinal center DLBCL with mutated EZH2, FL with wild-type EZH2 and FL with mutated EZH2. We expect to enroll approximately 30 patients in each trial arm, for a total of approximately 150 patients, assuming each arm of the study achieves its primary response rate goal in its first stage. We expect to disclose data from the germinal center DLBCL with wild-type EZH2 and non-germinal center B-cell DLBCL trial arms in mid-2016 and from the FL with wild-type EZH2 trial arm in the first half of 2017. We will not be able to reasonably estimate the

timing of the mutated EZH2 arms until we have completed an initial evaluation of enrollment rates; however, we expect that enrollment in these trial arms will be slower than the wild-type EZH2 arms based on the estimated incidence of mutated EZH2.

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The primary objective of the Phase 2 clinical trial will be to assess the objective response rate of EPZ-6438 in patients who have confirmed relapsed or refractory DLBCL or FL. The secondary objectives of the Phase 2 clinical trial will be to assess duration of response and progression-free survival of EPZ-6438 as a monotherapy.

It is important to note that the objective responses and treatment effects observed in the dose escalation portion of the study were experienced by only some of the lymphoma and INI1-deficient tumor patients enrolled in the trial, were observed in an open-label setting and might not be experienced by other patients treated with EPZ-6438. Additionally, the disease did progress in other lymphoma and INI1-deficient tumor patients enrolled in the dose escalation study. This Phase 1/2 trial is not designed to show results with statistical significance. Statistical significance means that an effect is unlikely to have occurred by chance. Clinical trial results are considered statistically significant when the probability of the results occurring by chance, rather than from the efficacy of the drug candidate, is sufficiently low. Since the trial is not powered to show results with statistical significance, the results from the trial may be attributable to chance and not the clinical efficacy of EPZ-6438. We plan to design any later stage trials that are intended to support marketing approval applications to show statistical significance. We would do so by enrolling a larger number of patients than enrolled in earlier trials.

We plan to launch the Phase 2 portion of our EPZ-6438 trial in non-Hodgkin B-cell lymphoma in the second quarter of 2015 in the European Union.

In the course of our ongoing preclinical safety studies for EPZ-6438, we observed the development of lymphoma in a single study in Sprague Dawley rats. We did not observe this finding in our parallel preclinical safety studies of EPZ-6438, which were conducted in primates. Additionally, we have not observed any similar findings in our ongoing Phase 1/2 clinical study of EPZ-6438. We have informed the relevant European regulatory authorities and the clinical investigators of this finding. We continued to enroll patients in the expansion cohorts of our Phase 1 study in France, with updated data from the dose escalation patients expected in mid-2015 and data on the expansion cohort patients expected by the end of 2015.

Expansion of trials of EPZ-6438 to the United States will require that we submit an investigational new drug application, or IND, 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 Phase 1/2 clinical study. We are in discussions with the FDA, and we are conducting additional preclinical studies to understand this observation more fully, prior to submitting our IND. If we are unable to adequately address this matter, we may be unable to expand our planned clinical trials of EPZ-6438 into the United States, our trials may be limited to certain patient populations or our ability to conduct trials in the United States may be delayed.

In the second half of 2015, we plan to initiate a Phase 1 trial of EPZ-6438 for the treatment of INI1-deficient tumors, such as MRT, in pediatric patients and a Phase 2 trial of EPZ-6438 for the treatment of INI1-deficient tumors, such as synovial sarcoma, in adult patients. These trials will only enroll patients with the targeted disease. The Phase 1 trial is currently designed to evaluate the safety, tolerability and preliminary efficacy of EPZ-6438 and to determine its maximum tolerated dose in children. The Phase 2 trial is currently designed to provide an initial assessment of efficacy, or proof-of-concept, in this adult patient population. We also plan to initiate in 2015 standard clinical pharmacology studies designed to evaluate the food effects and any potential drug-to-drug interactions of EPZ-6438.

Companion Diagnostic. We are working with Roche to develop an *in vitro* based diagnostic for use as a companion diagnostic with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations and plan to use this diagnostic in the prospective screening of patients for stratification in the Phase 2 portion of our EPZ-6438 clinical trial. The agreement with Roche calls for the development of a diagnostic to test for the presence of an oncogenic point mutation in EZH2. Under the agreement, Roche will have the right to commercialize the companion diagnostic

with EPZ-6438. We anticipate that we and Roche will coordinate our marketing and sales

activities for EPZ-6438 and the companion diagnostic. We have not yet determined whether companion diagnostics will be necessary for the INI1-deficient tumors as the EZH2 sensitivity may be inherent in the clinical diagnosis for most of the patient population.

EPZ-5676 DOT1L Inhibitor

Overview. We are developing EPZ-5676 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 EPZ-5676 using our proprietary product platform and initiated a Phase 1 clinical trial of this product candidate in September 2012. The dose escalation portion of this trial included patients with advanced hematologic malignancies, including, but not restricted to patients with alterations involving the *MLL* gene. The dose escalation was fully enrolled as of December 31, 2013, and, from December 2013 to November 2014, we enrolled patients in a 90 mg/m^2/day expansion cohort in the Phase 1 trial. The expansion cohort only included patients with MLL-r or MLL-PTD. Based on the results seen through the 90 mg/m^2/day expansion cohort, in January 2015, we initiated enrollment of adult MLL-r patients in a 54 mg/m^2/day expansion cohort to gain further clinical experience at this dose level. We chose this dose level based on complete responses observed in MLL-r patients at this dose level in the dose escalation portion of the Phase 1 trial.

In May 2014, we initiated a Phase 1 trial of EPZ-5676 in pediatric patients with MLL-r. This Phase 1 study is designed to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of EPZ-5676 in patients between the ages of three months and 18 years. This trial is also designed to provide a preliminary assessment of efficacy.

We retain all U.S. rights to EPZ-5676. We have granted Celgene an exclusive license to EPZ-5676 outside of the United States.

In August 2013, we were granted orphan drug designation for EPZ-5676 for the treatment of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL, by the FDA, and in January 2014, the European Commission granted orphan drug designation for EPZ-5676 for the treatment of AML and ALL.

Phase 1 Clinical Trial in Adult Patients. Our Phase 1 clinical trial of EPZ-5676 is a first-in-human open label, multicenter trial that is being conducted in two parts. The first part involves dose escalation in patients with advanced hematologic malignancies, including, but not restricted to, MLL-r patients. The second part involves expansion cohorts that only enroll MLL-r patients. We are currently enrolling a second expansion cohort of up to 20 MLL-r patients at a dose of 54 mg/m^2/day using an uninterrupted administration schedule and expect to disclose top-line data from this expansion cohort in the second half of 2015. We are currently conducting this trial at seven sites in the United States and one site in the European Union.

The primary objectives of the trial are to evaluate the safety and tolerability of EPZ-5676 and to determine its maximum tolerated dose. Secondary objectives of this trial are to:

- determine the pharmacokinetics of EPZ-5676;

assess the biochemical and physiological effects of EPZ-5676 on the human body, which is referred to as pharmacodynamics, including methylation in peripheral blood mononuclear cells and leukemia cells; and

evaluate preliminary anti-tumor activity in patients with MLL-r.

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Dose Escalation. We began enrolling patients in the dose escalation portion of the Phase 1 trial in September 2012 and completed enrollment in December 2013. A total of 25 patients were enrolled in one of six dose cohorts at dose levels of 12, 24, 36, 54, 80, or 90 mg/m^2/day, with patients in the 12, 24, 36, and 54 mg/m^2/day dose cohorts receiving EPZ-5676 on a 21-day on drug, seven-day off drug schedule via continuous intravenous administration and patients in the 80 and 90 mg/m^2/day dose cohorts receiving continued intravenous administration without a drug holiday. The dose escalation allowed for, but did not require, the enrollment of patients with the targeted MLL-r genetic alterations. The majority of patients had a diagnosis of AML. Other diagnoses included ALL and chronic myelomonocytic leukemia, or CMML. In December 2013, two patients in the 54 mg/m^2/day dose cohort of the dose escalation achieved complete responses. Based on preclinical data suggesting greater biological activity of uninterrupted drug exposure, these patients were switched from the original intravenous administration schedule, which included a seven-day drug holiday, to an uninterrupted intravenous administration schedule. One of these patients was diagnosed with AML with an MLL-r translocation. The other patient was diagnosed with CMML with an MLL-r translocation.

During the dose escalation portion of the trial, in addition to the two objective responses, we observed treatment effects of EPZ-5676 in other patients with MLL-r, such as treatment-related leukocytosis, cellular differentiation and maturation in blood and bone marrow and resolution of leukemia-related symptoms such as cachexia, fevers, and leukemia cutis that are consistent with anti-leukemic effects in MLL-r patients.

Expansion Cohorts. We enrolled 17 MLL-r patients in an expansion cohort at 90 mg/m^2/day from December 2013 to November 2014. These patients received EPZ-5676 with uninterrupted intravenous administration. Of the 17 patients enrolled in the 90 mg/m^2/day expansion cohort, one patient achieved a partial response.

The patients enrolled into the dose escalation cohorts and 90 mg/m^2/day expansion cohort were heavily pre-treated. Of the 42 patients enrolled through these two stages, 29 had received two or more prior therapies. Sixteen of the 42 patients had received at least one prior allogeneic hematopoietic cell transplant.

In the trial results to date, EPZ-5676 has exhibited a favorable safety and tolerability profile. Specifically, two dose-limiting toxicities in 23 total patients treated at the 90 mg/m^2/day dose level have been reported. Leukocytosis, an elevated white blood cell count, has been observed in some patients and is considered treatment-related, but consistent with the therapeutic mechanism of action of EPZ-5676, thus is not considered an adverse event.

The Phase 1 clinical trial is not powered to demonstrate efficacy with statistical significance. However, pending the results of this Phase 1 clinical trial, we plan to use the results of the trial to design any later stage trials that are intended to demonstrate statistical significance and potentially support marketing approval applications. We would do so by enrolling a larger number of patients than enrolled in earlier trials.

Based on the collective findings of the dose escalation experience, and especially that of the 54 mg/m^2/day dose cohort, we have initiated a second expansion cohort, at 54 mg/m^2/day, in 2015, to gain more experience at this dose level. This planned expansion cohort will enroll up to an additional 20 MLL-r patients.

Phase 1 Clinical Trial in Pediatric Patients. In May 2014, we initiated a Phase 1 clinical trial of EPZ-5676 in pediatric patients. This clinical trial is restricted to pediatric patients with MLL-r acute leukemia and is similar in design to the adult trial, with a dose escalation and an expansion cohort that we would expect will enable us to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of EPZ-5676 in patients between the ages of three months and 18 years and also provide a preliminary assessment of efficacy. Patients in this trial are receiving uninterrupted administration of EPZ-5676. We expect to complete enrollment in this Phase 1 trial in the second half of 2015.

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Companion Diagnostic. We are currently relying on commercially available diagnostics that are commonly used by clinicians to identify and diagnose MLL-r patients.

HMT Collaborations

We have entered into three strategic collaborations for our therapeutic programs. These therapeutic collaborations have provided us with $188.7 million in non-equity funding through December 31, 2014. In addition, as of December 31, 2014, we were owed an additional $2.1 million under these collaborations for research and development services revenue earned and global development co-funding. Our therapeutic 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

In April 2012, we entered into a collaboration and license agreement with Celgene to discover, develop and commercialize, in all countries other than the United States, small molecule HMT inhibitors targeting DOT1L, including EPZ-5676, and any other HMT targets from our product platform, excluding the EZH2 HMT and targets covered by our GSK collaboration, which we refer to as the available targets.

Under the terms of the agreement, we received a $65.0 million upfront payment 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 $68.0 million. In addition, we recorded a $25.0 million clinical development milestone payment and $5.8 million of global development co-funding through December 31, 2014. We are also eligible to earn up to $35.0 million in additional clinical development milestone payments and up to $100.0 million in regulatory milestone payments related to DOT1L as well as up to $65.0 million in payments, including a combination of clinical development milestone payments and an option exercise fee, and up to $100.0 million in regulatory milestone payments for each available target as to which Celgene exercises its option during an initial option period ending in July 2015. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment. As to DOT1L and each available target as to which Celgene may exercise its option, we retain all product rights in the United States and are eligible to receive royalties for each target at defined percentages ranging from the mid-single digits to the mid-teens on net product sales outside of the United States, subject to reductions in specified circumstances.

GlaxoSmithKline

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, 2014, we also received $6.0 million of fixed research funding, $15.0 million of preclinical research and development milestone payments and

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$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.

Eisai

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 EPZ-6438. Under the amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization outside of Japan of EPZ-6438 and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture EPZ-6438 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 EPZ-6438, 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, 2014, for total consideration received from Eisai of $38.7 million. 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 will be solely responsible for funding global development, manufacturing and commercialization costs for EZH2 compounds outside of Japan, and Eisai will be 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 have agreed upon a transition to us of ongoing development and manufacturing activities 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.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the Risk Factors section of this prospectus supplement immediately following this prospectus supplement summary. These risks include the following:

We have incurred significant losses since our inception. Our accumulated deficit was $111.1 million as of December 31, 2014, representing our cumulative losses since our inception in 2007. We expect to incur losses over the next several years and may never achieve or maintain profitability.

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.

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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 scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. We believe we are the first company to conduct clinical trials of HMT inhibitors and demonstrate objective responses in patients in such a trial.

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, it is important to note that the objective responses observed in our dose escalation clinical trials of EPZ-6438 and EPZ-5676 were achieved in a limited number of patients, were observed in an open-label setting, are not statistically significant and might not be achieved by any other patient treated with these product candidates in these trials.

The outcome of preclinical safety studies may delay the launch of or enrollment in future clinical trials. For example, prior to commencing clinical trials of EPZ-6438 in the United States, we will need to submit an IND and address 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 Phase 1/2 clinical study, the development of lymphoma in Sprague Dawley rats that we observed in one of our preclinical safety studies.

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.

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

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.

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.

Company 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 and our telephone number is (617) 229-5872. Our website address is www.epizyme.com. The information contained on, or that can be accessed through, our website is not a part of this prospectus supplement. We have included our website

address in this prospectus supplement solely as an inactive textual reference.

Epizyme® and the Epizyme logo are our registered trademarks. The other trademarks, trade names and service marks appearing in this prospectus supplement are the property of their respective owners.

Implications of Being an Emerging Growth Company

As a company with less than $1 billion in revenue during our last fiscal year, we qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain

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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 will remain an emerging growth company until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2018; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission based on the market value of our common stock held by non-affiliates. If the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30, 2015, we would cease to be an emerging growth company as of the end of 2015.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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The Offering

Common Stock offered by Epizyme	6,000,000 shares.
Common Stock to be outstanding after this offering	40,472,071 shares.
Option to purchase additional shares	The underwriters have an option to purchase up to an additional 900,000 shares of our common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of Proceeds	We estimate that the net proceeds to us from this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately $116.7 million, or approximately $134.2 million if the underwriters exercise their option to purchase additional shares from us in full. We plan to use the net proceeds from this offering, together with our existing cash and cash equivalents, to fund our ongoing and planned clinical trials of EPZ-6438 and EPZ-5676, to fund research and development to advance our pipeline of preclinical product candidates and expand our product platform, and for working capital and other general corporate purposes. See Use of Proceeds.
Risk Factors	You should read the Risk Factors section of this prospectus supplement beginning on page S-19 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
NASDAQ Global Market symbol	EPZM

The number of shares of our common stock to be outstanding after this offering is based on the 34,472,071 shares of our common stock outstanding as of March 6, 2015 and excludes:

- 3,578,475 shares of common stock issuable upon the exercise of stock options outstanding as of March 6, 2015, at a weighted average exercise price of $12.63 per share; and
- 6,373,717 shares of common stock available for future issuance under our equity compensation plans as of March 6, 2015.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares of our common stock.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should carefully consider the risks and uncertainties described below together with all other information contained in this prospectus supplement, the accompanying prospectus and in our filings with the SEC that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. If any of the following risks actually occurs, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

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, very few drugs premised on epigenetics have been discovered. Moreover, those drugs based on an epigenetic mechanism that have received marketing approval are in a different target class than HMTs, where our research and development is focused. Although preclinical studies suggest that genetic alterations in HMTs cause them to drive particular human cancers, 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.

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 of our efforts and financial resources in the identification and preclinical and clinical development of HMT inhibitors. 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;

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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 product platform to build a pipeline of product candidates.

A key element of our strategy is to use and expand our product platform to build a pipeline of small molecule inhibitors of HMT 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 at specific HMT targets, we may not be able to develop product candidates that are safe and effective HMT 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.

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 early 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 ongoing preclinical safety studies of EPZ-6438, we observed the development of lymphoma in a single study in Sprague Dawley rats. We have informed the relevant European regulatory authorities, the FDA and the clinical investigators of this finding in rats, and are in active discussions with the regulatory authorities. Expansion of trials of EPZ-6438 to the United States will require that we submit an IND 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 Phase 1/2 clinical study. If we are unable to adequately address this matter, we may be unable to expand our planned clinical trials of EPZ-6438 into the United States, our trials may be limited to certain patient populations or our ability to conduct 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 MLL-r patients in the fourth dose cohort of the dose escalation portion of our Phase 1 clinical

trial of EPZ-5676 were observed in only two of the MLL-r patients enrolled in the trial through the first expansion cohort of the Phase 1 trial, were achieved in an open-label setting, are not statistically significant and might not be achieved by any other patient treated with EPZ-5676. 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 as a result of 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;
- 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;

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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 United States Food and Drug Administration, or 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.

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.

Following our general product development strategy, we have designed our ongoing clinical trials of EPZ-6438 and EPZ-5676, and expect to design future trials, to include some patients with the applicable genetic alteration that we believe causes the disease with a view to assessing possible early evidence of potential therapeutic effect. If we are unable to include patients with the applicable genetic alteration, this could compromise our ability to seek participation in FDA expedited review and approval programs, including breakthrough therapy and fast track designation, or otherwise to seek to accelerate clinical development and regulatory timelines.

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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.

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 intend to 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 expect that, at least in some cases, the FDA and similar regulatory authorities outside of the United States may require the development and regulatory approval of a companion diagnostic as a condition to approving our therapeutic product candidates. 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 EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations.

We may seek to enter into similar agreements for our other therapeutic product candidates and possible expansion indications. 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 we, or 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

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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 $55.0 million for the year ended December 31, 2014. As of December 31, 2014, we had an accumulated deficit of $111.1 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 preclinical studies and, beginning in 2012, clinical trials. We are still in the early stages of development of our product candidates, and we have not completed development of any drugs. 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 increase substantially over the next several years as we:

assume responsibility from Eisai for the ongoing Phase 1/2 clinical trial of EPZ-6438 for treatment of patients with non-Hodgkin lymphoma and solid tumors;

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

initiate our planned clinical trials of EPZ-6438 in adult and pediatric patients with INI1-deficient tumors;

continue our Phase 1 clinical trial of EPZ-5676 for treatment of adult patients with MLL-r;

continue our Phase 1 clinical trial of EPZ-5676 in pediatric patients with MLL-r;

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.

In addition, 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 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. In addition, we are responsible for solely funding global development, manufacturing and commercialization costs for EZH2 compounds. Prior to the amended and restated agreement, Eisai was responsible for solely funding all research, development and commercialization costs for licensed compounds.

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To become and remain profitable, we must succeed in developing, and eventually commercializing, 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 you to lose all or part of your 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 as we assume control of the EZH2 program from Eisai, pay the upfront and any milestone payments provided for and achieved under the amended and restated collaboration and license agreement and assume responsibility for the funding of the program moving forward, including our ongoing Phase 1/2 clinical trial of EPZ-6438; initiate our planned clinical trials of EPZ-6438 in adult and pediatric patients with INI1-deficient tumors; initiate our planned clinical pharmacology studies of EPZ-6438; continue the Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and the Phase 1 clinical trial of EPZ-5676 in pediatric patients with MLL-r; 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 the net proceeds to us from this offering, together with our existing cash and cash equivalents and development co-funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2016, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. 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 research funding and achieve milestones under these agreements;

the progress and results of our ongoing Phase 1/2 clinical trial of EPZ-6438 and Phase 1 clinical trials of EPZ-5676 and our planned trials of EPZ-6438;

the number and development requirements of additional indications for EPZ-6438 and EPZ-5676 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;

- the costs, timing and outcome of regulatory review of our product candidates;
- 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 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. We do not have any committed external source of funds other than research funding under our existing collaborations. 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 1/2 clinical trial of EPZ-6438 and Phase 1 clinical trials of EPZ-5676 but have not completed enrollment in any of these trials. 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

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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, as a young business, 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.

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. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our 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.

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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, 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.

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. In addition, many companies are

developing cancer therapeutics that work by targeting epigenetic mechanisms other than HMTs, and some companies, including Celgene and Eisai, are marketing such treatments. There are also a number of companies that we believe are developing new epigenetic treatments for cancer that target HMTs, including GSK, Novartis AG, Pfizer, Inc. and Genentech, Inc.

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 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.

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 $5.0 million in product liability insurance coverage in the aggregate, with a per incident limit of $5.0 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.

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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 rights under our amended and restated collaboration and license agreement with Eisai, we no longer have access to such capabilities for EPZ-6438. 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;
- 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.

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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 prospectus 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. In addition, under our collaboration agreement with Celgene, during the option period specified in the agreement, which could extend to July 2016, Celgene has the right to exercise its option to acquire a license to additional targets other than DOT1L until the effectiveness of an investigational new drug application, or IND, for an HMT inhibitor directed to such additional target. This option effectively covers all HMT targets, other than EZH2, that are not currently subject to our GSK collaboration. As a result, our ability to enter into collaboration agreements for additional HMT targets is significantly limited until the end of the option period under the Celgene agreement and may continue to be limited after that time depending on how many targets Celgene elects to license, if any. 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.

As a component of the amended and restated collaboration agreement with Eisai, we have entered into a transition plan with Eisai under which we will coordinate the transition of clinical and related development and manufacturing responsibilities from Eisai. The transition of these activities, including the time necessary to transfer regulatory sponsorship of our ongoing Phase 1/2 clinical trial; transfer or establish clinical site agreements for our ongoing Phase 1/2 clinical trial; and identify, test and establish manufacturing capabilities with a third party manufacturer, among other things, could cause delays in the clinical progress and development of EPZ-6438.

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 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.

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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 1/2 clinical trial of EPZ-6438 and our ongoing Phase 1 clinical trials of EPZ-5676 and 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;
- 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.

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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.

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.

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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.

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.

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 a license agreement and a research agreement 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 agreement. 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.

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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.

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

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, 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 received approval to market any of our product candidates from regulatory authorities in any 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. 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 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 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.

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.

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 European exclusivity period 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. 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 some 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

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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.

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 international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union and many other jurisdictions, 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, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties 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.

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 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,

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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 closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers communications regarding off-label use, and if we 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 relating to the promotion of prescription drugs may lead to investigations 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;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;

suspension or withdrawal of marketing approvals;

refusal to permit the import or export of our products;

product seizure; or

injunctions or the imposition of civil or criminal penalties.

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 customers 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

third party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we 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 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 civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

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

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

- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, with data collection beginning in August 2013; and

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

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government 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.

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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.

More recently, in March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the PPACA, 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;
- 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 new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;

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

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

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

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

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These 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.

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.

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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 development expertise of Robert J. Gould, Ph.D., our President and Chief Executive Officer, Andrew E. Singer, our Executive Vice President of Finance and Administration and Chief Financial Officer, Robert A. Copeland, Ph.D., our President of Research and Chief Scientific Officer, and Peter T.C. Ho, M.D., Ph.D., our Chief Development Officer, as well as the other principal members of our management, scientific and clinical team. 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.

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 and This Offering

After this offering our executive officers and directors and their affiliates, if they choose to act together, will continue to have the ability to significantly influence all matters submitted to stockholders for approval.

Upon the closing of this offering our executive officers and directors and their affiliates will beneficially own, in the aggregate, shares representing approximately 31.6% of our common stock, assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of March 6, 2015. As a result, following this offering, if these stockholders were to choose to act together, they

would 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, would 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.

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.

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Some provisions in our collaboration agreement with Celgene could deter potential buyers of our company from proposing an acquisition and could make us a less attractive target for them. These provisions include the following:

We granted Celgene an exclusive license, for all countries other than the United States, to HMT inhibitors directed to DOT1L and an option, on a target-by-target basis, to exclusively license, for all countries of the world other than the United States, rights to HMT inhibitors directed to any other HMT targets during the option period, excluding the EZH2 HMT and targets covered by our GSK collaboration. During the option period specified in the agreement, which could extend until July 2016, Celgene has the right to exercise its option to license non-U.S. rights to additional targets other than DOT1L until the effectiveness of an IND for an HMT inhibitor directed to such additional target. The decision to exercise the options for available targets is in Celgene s sole discretion.

Under our collaboration agreement with Celgene, we granted to Celgene a right of first negotiation with respect to business combination transactions that we may desire to pursue with third parties during the option period, including any extension of this period. During the option period, we are required to notify Celgene if we desire to pursue a specified business combination transaction with a third party prior to negotiating terms with the third party, and after so notifying Celgene, we have agreed not to, directly or indirectly, solicit, initiate or encourage proposals from, discuss or negotiate with, or provide any information to, any third party related to the proposed transaction for a specified period from the date we first notify Celgene of such proposed transaction, or the Celgene negotiation period. If Celgene notifies us that it is interested in entering into the proposed transaction, we have agreed to negotiate in good faith with Celgene during the Celgene negotiation period. Following the Celgene negotiation period, if we have not entered into the proposed transaction with Celgene, or if Celgene does not notify us that it is interested in entering into the proposed transaction, we are free to enter into the proposed transaction with a third party for a period of 225 days following the expiration of the Celgene negotiation period, but we are obligated to re-offer the proposed transaction to Celgene if, during the option term, we propose to enter into the proposed transaction with a third party on terms that, in specified respects, are less favorable to us than the terms last offered by Celgene.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

The price of our common stock in this offering is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. To the extent outstanding options are exercised, you will incur further dilution. Based on the public offering price of $20.75 per share, you will experience immediate dilution of $13.90 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering and the public offering price.

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

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 you to sell your shares, including shares you may purchase in this offering, without depressing the market price for the shares or sell your 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. From May 31, 2013 to March 6, 2015, the sale price of our common stock as reported on the NASDAQ Global Market ranged from a high of $45.72 per share

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to a low of $16.51 per share. 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. The market price for our common stock may be influenced by many factors, including:

- the success of competitive products or technologies;
- 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, including the net proceeds we receive in this offering, and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents, including the net proceeds we receive in this offering, 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.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Upon completion of this offering, based on our shares outstanding as of March 6, 2015, we will have 40,472,071 shares of common stock outstanding, assuming no exercise of the underwriters option to purchase additional shares of common stock. Of these shares, 12,158,440 are subject to a contractual lock-up with the underwriters for this offering for a period of 45 days following this offering. These shares can be sold, subject to any applicable volume limitations under federal securities laws, after the earlier of the expiration of, or release from, the 45-day lock-up period. The balance of our outstanding shares of common stock, including any shares purchased in this offering, may be resold into the public market immediately without restriction, unless owned or purchased by our affiliates. Moreover, after this offering, certain holders of our common stock will

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have the right, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

As of March 6, 2015, there were 9,952,192 shares subject to outstanding options or that are otherwise issuable under our equity compensation plans, all of which shares we have registered under the Securities Act of 1933, as amended, on registration statements on Form S-8. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described above, to the extent applicable.

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 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

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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 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.

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USE OF PROCEEDS

We estimate that the net proceeds to us from our issuance and sale of shares of our common stock in this offering will be approximately $116.7 million, or approximately $134.2 million if the underwriters exercise their option to purchase additional shares in full, in each case after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of December 31, 2014, we had cash and cash equivalents of $190.1 million. We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents, as follows:

- to fund global development costs of EPZ-6438 outside of Japan, including the costs of the planned Phase 2 portion of our Phase 1/2 clinical trial in patients with relapsed or refractory B-cell lymphoma, our planned Phase 2 trial in adult patients with INI1-deficient tumors, our planned Phase 1 trial in pediatric patients with INI1-deficient tumors, and our planned clinical pharmacology studies of EPZ-6438;

- to fund our two ongoing Phase 1 clinical trials of EPZ-5676;

- to fund research and development costs to advance our pipeline of preclinical product candidates and expand our product platform; and

- for working capital and other general corporate purposes.

This expected use of our net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We may find it necessary or advisable to use the net proceeds from this offering for other purposes, and we will have broad discretion in the application of net proceeds.

Based on our planned use of our net proceeds from this offering described above, we estimate that such funds, together with our existing cash and cash equivalents as of December 31, 2014 and development co-funding that we expect to receive under our existing collaborations, will enable us to fund our operations and capital expenditure requirements through at least the end of 2016, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. We expect that prior to such time, with these cash resources, we will be able to complete at least the germinal center DLBCL with wild-type EZH2 and non-germinal center DLBCL arms of the Phase 2 portion of our Phase 1/2 clinical trial of EPZ-6438, as well as our planned clinical pharmacology studies of EPZ-6438 and our two ongoing Phase 1 clinical trials of EPZ-5676.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

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PRICE RANGE OF COMMON STOCK

Our common stock began trading on The NASDAQ Global Market under the symbol EPZM on May 31, 2013. Prior to that time, there was no public market for our common stock. The following table sets forth, for the quarterly periods indicated, the high and low intraday sale price per share of our common stock, as reported on The NASDAQ Global Market.

	High	Low
Year ended December 31, 2013		
Second Quarter (from May 31, 2013)	$ 30.86	$ 18.60
Third Quarter	$ 45.72	$ 26.06
Fourth Quarter	$ 42.71	$ 18.10
Year ended December 31, 2014		
First Quarter	$ 41.23	$ 19.76
Second Quarter	$ 31.35	$ 18.75
Third Quarter	$ 40.98	$ 25.10
Fourth Quarter	$ 30.26	$ 16.51
Year ended December 31, 2015		
First Quarter (through March 17, 2015)	$ 25.48	$ 16.63

On March 17, 2015, the last sale price of our common stock, as reported on The NASDAQ Global Market, was $21.13 per share.

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DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain earnings, if any, to finance the growth and development of our business. We do not expect to pay any cash dividends on our common stock in the foreseeable future. Payment of future dividends, if any, will be at the discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements, restrictions contained in current or future financing instruments, provisions of applicable law and other factors the board deems relevant.

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DILUTION

If you invest in our common stock in this offering, your interest will be diluted immediately to the extent of the difference between the public offering price per share you will pay in this offering and the as adjusted net tangible book value per share of our common stock after this offering. Our historical net tangible book value as of December 31, 2014 was $160.3 million, or $4.66 per share of common stock. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding on December 31, 2014.

After giving effect to our issuance and sale of 6,000,000 shares of common stock in this offering at the public offering price of $20.75 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of December 31, 2014 would have been $277.0 million, or $6.85 per share. This represents an immediate increase of $2.19 in as adjusted net tangible book value per share to existing stockholders and immediate dilution of $13.90 in as adjusted net tangible book value per share to new investors purchasing common stock in this offering. Dilution per share to new investors is determined by subtracting as adjusted net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this per share dilution to the new investors purchasing shares of common stock in this offering without giving effect to any exercise by the underwriters of their option to purchase additional shares:

Public offering price per share		$ 20.75
Net tangible book value per share as of December 31, 2014	$ 4.66	
Increase per share attributable to sale of shares of common stock in this offering	2.19	
As adjusted net tangible book value per share after this offering		6.85
Dilution per share to new investors		$ 13.90

If the underwriters exercise their option to purchase 900,000 additional shares in full at the public offering price of $20.75 per share, the as adjusted net tangible book value will increase to $7.13 per share, representing an immediate increase to existing stockholders of $2.47 per share and an immediate dilution of $13.62 per share to new investors. If any shares are issued upon exercise of outstanding options at prices below the public offering price, you will experience further dilution.

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MATERIAL U.S. FEDERAL TAX CONSIDERATIONS

The following is a general discussion of the material U.S. federal income and estate tax considerations applicable to non-U.S. holders with respect to their ownership and disposition of shares of our common stock. This discussion is for general information only and is not tax advice. Accordingly, all prospective non-U.S. holders of our common stock should consult their own tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of the purchase, ownership and disposition of our common stock. For purposes of this discussion, a non-U.S. holder means a beneficial owner of our common stock who is not for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation or any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (1) a U.S. court is able to exercise primary supervision over the trust s administration and one or more U.S. persons have the authority to control all of the trust s substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus supplement, all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus supplement. We assume in this discussion that a non-U.S. holder holds shares of our common stock as a capital asset, generally property held for investment.

This discussion does not address all aspects of U.S. federal income and estate taxation, including the Medicare contribution tax, that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder s individual circumstances nor does it address any aspects of U.S. state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

- insurance companies;
- tax-exempt organizations;
- financial institutions;

brokers or dealers in securities;

regulated investment companies;

pension plans;

controlled foreign corporations;

passive foreign investment companies;

owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment; and

certain U.S. expatriates.

In addition, this discussion does not address the tax treatment of partnerships or persons who hold our common stock through partnerships or other pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of acquiring, holding and disposing of our common stock through a partnership or other pass-through entity, as applicable.

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There can be no assurance that the Internal Revenue Service, which we refer to as the IRS, will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain, a ruling from the IRS with respect to the U.S. federal income or estate tax consequences to a non-U.S. holder of the purchase, ownership or disposition of our common stock.

Distributions on Our Common Stock

Distributions on our common stock generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder s investment, up to such holder s tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock. Any such distributions will also be subject to the discussion below under the section titled Withholding and Information Reporting Requirements FATCA.

Dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder s country of residence. If we determine, at a time reasonably close to the date of payment of a distribution on our common stock, that the distribution will not constitute a dividend because we do not anticipate having current or accumulated earnings and profits, we intend not to withhold any U.S. federal income tax on the distribution as permitted by U.S. Treasury Regulations. If we or another withholding agent withholds tax on such a distribution, a non-U.S. holder may be entitled to a refund of the tax withheld, which the non-U.S. holder may claim by timely filing the required information with the IRS.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is generally taxed at the same graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder s country of residence.

A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder s country of residence generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or successor form) and satisfy applicable certification and other requirements. Non-U.S. holders are urged to consult their tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing the required information with the IRS.

Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock

In general, a non-U.S. holder will not be subject to any U.S. federal income tax on any gain realized upon such holder s sale, exchange or other taxable disposition of shares of our common stock unless:

the gain is effectively connected with the non-U.S. holder s conduct of a U.S. trade or business and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed base maintained by such non-U.S. holder in the United States, in which case the non-U.S. holder generally

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will be taxed at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above in Distributions on Our Common Stock also may apply;

the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the taxable disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder s country of residence) on the net gain derived from the taxable disposition, which may be offset by certain U.S. source capital losses of the non-U.S. holder, if any; or

we are, or have been, at any time during the five-year period preceding such taxable disposition (or the non-U.S. holder s holding period, if shorter) a U.S. real property holding corporation, unless our common stock is regularly traded on an established securities market and the non-U.S. holder holds no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the 5-year period ending on the date of the taxable disposition or the period that the non-U.S. holder held our common stock. If we are determined to be a U.S. real property holding corporation and the foregoing exception does not apply, then a purchaser may withhold 10% of the proceeds payable to a non-U.S. holder from a sale of our common stock and the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code). Generally, a corporation is a U.S. real property holding corporation only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we do not believe that we are, or have been, a U.S. real property holding corporation, or that we are likely to become one in the future. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rules described above.

U.S. Federal Estate Tax

Shares of our common stock that are owned or treated as owned at the time of death by an individual who is not a citizen or resident of the United States, as specifically defined for U.S. federal estate tax purposes, are considered U.S. situs assets and will be included in the individual s gross estate for U.S. federal estate tax purposes. Such shares, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

Backup Withholding and Information Reporting

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to dividends on our common stock. Dividends paid to non-U.S. holders subject to the U.S. withholding tax, as described above in Distributions on Our Common Stock, generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a

non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a

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non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder s U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Withholding and Information Reporting Requirements FATCA

The Foreign Account Tax Compliance Act, or FATCA, will impose a U.S. federal withholding tax at a rate of 30% on payments of dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to certain foreign entities, unless (i) if the foreign entity is a foreign financial institution, such foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the foreign entity is not a foreign financial institution, such foreign entity identifies certain of its U.S. investors, if any, or (iii) the foreign entity is otherwise exempt under FATCA. Under applicable U.S. Treasury Regulations, withholding under FATCA currently applies to payments of dividends on our common stock and is scheduled to apply to gross proceeds from a sale or other disposition of our common stock made after December 31, 2016. Under certain circumstances, a non-U.S. holder may be eligible for refunds or credits of the tax. Certain intergovernmental agreements between the United States and other countries may modify these rules. Non-U.S. holders should consult their own tax advisors regarding the possible implications of this legislation on their investment in our common stock and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

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UNDERWRITING

Leerink Partners LLC, Cowen and Company, LLC and RBC Capital Markets LLC are acting as joint book-running managers for this offering. Leerink Partners LLC and Cowen and Company, LLC are acting as representatives of each of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus supplement, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
Leerink Partners LLC	1,950,000
Cowen and Company, LLC	1,800,000
RBC Capital Markets, LLC	900,000
JMP Securities LLC	750,000
SunTrust Robinson Humphrey, Inc.	420,000
Mizuho Securities USA Inc.	180,000
Total	6,000,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of these shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officers certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover of this prospectus and to dealers at that price less a concession not in excess of $0.747 per share. After the initial offering, the public offering price, concession or any other term of the offering may be changed.

The following table shows the public offering price, underwriting discount and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares of our common stock.

	Per Share	Total Without Option	Total With Option
Public offering price	$ 20.75	$ 124,500,000	$ 143,175,000
Underwriting discount	$ 1.245	$ 7,470,000	$ 8,590,500
Proceeds, before expenses, to us	$ 19.505	$ 117,030,000	$ 134,584,500

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $350,000. We also have agreed to reimburse the underwriters for up to $35,000 for their FINRA counsel fee. In accordance with FINRA Rule 5110, this reimbursed fee is deemed underwriting compensation for this offering.

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Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus supplement, to purchase up to 900,000 additional shares at the public offering price, less the underwriting discount. If the underwriters exercise this option, each will be obligated, subject to conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter s initial amount reflected in the above table.

No Sales of Similar Securities

We and our officers and directors have agreed that, subject to specified limited exceptions, for a period of 45 days from the date of this prospectus supplement, we and they will not, without the prior written consent of Leerink Partners LLC and Cowen and Company, LLC, as representatives of the underwriters, offer, issue, sell, dispose of or hedge any shares of our common stock or any securities convertible into or exchangeable for our common stock. Leerink Partners LLC and Cowen and Company, LLC, in their sole discretion, may release any of the securities subject to these lock-up agreements at any time, which, in the case of officers and directors, shall be with notice.

NASDAQ Global Market Listing

Our common stock is listed on The NASDAQ Global Market under the symbol EPZM.

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representatives may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with the offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. Covered short sales are sales made in an amount not greater than the underwriters option described above. The underwriters may close out any covered short position by either exercising their option or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option granted to them. Naked short sales are sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the closing of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Similar to other purchase transactions, the underwriters purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might

otherwise exist in the open market. The underwriters may conduct these transactions on The NASDAQ Global Market, in the over-the-counter market or otherwise.

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Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

In connection with the offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

Some of the underwriters and their affiliates may in the future engage in investment banking and other commercial dealings in the ordinary course of business with us or our affiliates. They may in the future receive customary fees and commissions for these transactions.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers.

Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Selling Restrictions

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of shares may be made to the public in that Relevant Member State other than:

A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or

C. in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares shall require the Company or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer

have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

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We, the representatives and each of our and the representatives affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the company nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression an offer to the public in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression Prospectus Directive means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

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LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Certain legal matters related to this offering will be passed upon for the underwriters by Cooley LLP, Reston, Virginia. Cooley LLP has from time to time performed legal services for us.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2014, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our consolidated financial statements are incorporated by reference in reliance on Ernst & Young LLP s report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at http://www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at http://www.epizyme.com. Our website is not a part of this prospectus supplement and is not incorporated by reference in this prospectus supplement. You may also read and copy any document we file at the SEC s Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus supplement is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement and the accompanying prospectus regarding us and the securities, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC s internet site.

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INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference in this prospectus supplement and the accompanying prospectus much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying prospectus is considered to be part of this prospectus supplement and the accompanying prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement and the accompanying prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus supplement and the accompanying prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement, the accompanying prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus supplement and the accompanying prospectus incorporate by reference the documents listed below (File No. 001-35945) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2014;
- The information included in the Proxy Statement for the 2014 Annual Meeting of Stockholders, filed on April 30, 2014, to the extent incorporated by reference into Part III of the Annual Report on Form 10-K for the fiscal year ended December 31, 2013, filed on February 28, 2014;
- Current Reports on Form 8-K filed on February 3, 2015 and March 16, 2015; and
- The description of our common stock contained in our Registration Statement on Form 8-A filed on May 24, 2013, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or phone number:

400 Technology Square

Cambridge, Massachusetts 02139

Attn: Investor Relations

617-229-5872

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$200,000,000

PROSPECTUS

EPIZYME, INC.

Common Stock

Preferred Stock

Units

Warrants

Debt Securities

We may offer and sell securities from time to time in one or more offerings of up to $200,000,000 in aggregate offering price. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement before you invest.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Market under the symbol EPZM.

Investing in these securities involves certain risks. See Risk Factors included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is June 27, 2014

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, which we refer to as the SEC or the Commission , utilizing a shelf registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings for an aggregate initial offering price of up to $200,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading Where You Can Find More Information beginning on page 2 of this prospectus.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and any accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in this prospectus or such accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to we, our and us refer, collectively, to Epizyme, Inc., a Delaware corporation, and its consolidated subsidiary.

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WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at http://www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at http://www.epizyme.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus. You may also read and copy any document we file at the SEC s Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiary and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 001-35945) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of the initial registration statement and the effectiveness of the registration statement and following the effectiveness of the registration statement until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2013, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2014 Annual Meeting of Stockholders;

- Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2014;

- Current Reports on Form 8-K filed April 22, 2014 (solely with respect to Exhibits 10.1 and 10.2 therein) and June 11, 2014; and

- The description of our common stock contained in our Registration Statement on Form 8-A filed on May 24, 2013, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

400 Technology Square

Cambridge, Massachusetts 02139

Attn: Investor Relations

617-229-5872

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FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated by reference in this prospectus include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements may be identified by such forward-looking terminology as anticipate, believe, estimate, expect, intend, may, plan, predict, potential, will, would, could, should, continue, and similar 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 personalized therapeutics for patients with genetically defined cancers;
- our ongoing and planned clinical trials, including the timing of anticipated results;
- 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;
- our ability to identify additional products or product candidates with significant commercial potential that are consistent with our commercial objectives; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

You are cautioned that these forward-looking statements are only predictions and are subject to risks, uncertainties and assumptions that are referenced in the section of any accompanying prospectus supplement entitled Risk Factors. You should also carefully review the risk factors and cautionary statements described in the other documents we file from time to time with the SEC, specifically our most recent Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. 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 prospectus, 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 prospectus which modify or impact any of the forward-looking statements contained in this prospectus will be deemed to modify or supersede such statements in this prospectus.

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EPIZYME, INC.

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize innovative personalized therapeutics for patients with genetically defined cancers. We have built a proprietary product platform that we use to create small molecule inhibitors of a 96-member class of enzymes known as histone methyltransferases, or HMTs. Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. Our therapeutic strategy is to inhibit oncogenic HMTs to treat the underlying causes of the associated genetically defined cancers.

We are a leader in the translation of the science of epigenetics into first-in-class personalized therapeutics for patients with genetically defined cancers and currently have two HMT inhibitors in clinical development for the treatment of patients with genetically defined cancers. We believe we are the first company to conduct a clinical trial of an HMT inhibitor. We are conducting multiple clinical trials of our most advanced product candidate, EPZ-5676, an inhibitor targeting the DOT1L HMT, being developed for the treatment of acute leukemias with genetic alterations of the *MLL* gene, referred to as MLL-r or MLL-PTD. We are conducting a Phase 1 trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients, and a Phase 1b study of EPZ-5676 in MLL-r pediatric patients. We are also conducting a Phase 1/2 clinical trial of our second most advanced product candidate, EPZ-6438, an inhibitor targeting the EZH2 HMT, being developed for the treatment of a genetically defined subtype of non-Hodgkin lymphoma and solid tumors including INI1-deficient tumors such as synovial sarcoma and malignant rhabdoid tumors.

In addition to our clinical programs, we also have a pipeline of other HMT inhibitors that are in preclinical development that target our other prioritized HMTs. These programs are directed to genetically defined cancers, both hematological and solid tumors.

We have entered into strategic collaborations for certain of our therapeutic programs and corresponding companion diagnostics. Our three primary collaboration partners for our therapeutic programs are Celgene Corporation and Celgene International Sàrl; Eisai Co. Ltd., and Glaxo Group Limited, an affiliate of GlaxoSmithKline. We retain all product rights in the United States under the Celgene collaboration and an opt-in right to co-develop, co-commercialize and share profits as to licensed products in the United States under the Eisai collaboration.

Our principal executive offices are located at 400 Technology Square, Cambridge, Massachusetts 02139, and our telephone number is 617-229-5872.

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CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES

The following table sets forth our ratio of earnings to fixed charges and our coverage deficiency for each of the periods indicated. You should read this table in conjunction with the consolidated financial statements and notes incorporated by reference in this prospectus.

	Three Months Ended March 31, 2014	Fiscal Year Ended December 31, 2013	Fiscal Year Ended December 31, 2012	Fiscal Year Ended December 31, 2011
Net loss	$ (6,884)	$ (3,483)	$ (702)	$ (20,957)
Consolidated ratios of earnings to fixed charges(1)	N/A	N/A	N/A	N/A
Coverage deficiency	$ (6,884)	$ (3,483)	$ (702)	$ (20,957)

(1) We did not record earnings for the three months ended March 31, 2014 or for the years ended December 31, 2013, 2012 and 2011. Accordingly, our earnings were insufficient to cover fixed charges for such periods, and we are unable to disclose a ratio of earnings to fixed charges for such periods.

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USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include the acquisition of companies or businesses, repayment and refinancing of debt, if any, working capital and capital expenditures. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

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DESCRIPTION OF DEBT SECURITIES

We may offer debt securities which may be senior or subordinated. We refer to the senior debt securities and the subordinated debt securities collectively as debt securities. The following description summarizes the general terms and provisions of the debt securities. We will describe the specific terms of the debt securities and the extent, if any, to which the general provisions summarized below apply to any series of debt securities in the prospectus supplement relating to the series and any applicable free writing prospectus that we authorize to be delivered. When we refer to the Company, we, our, and us in this section, we mean Epizyme, Inc. excluding, unless the context otherwise requi or as otherwise expressly stated, our subsidiary.

We may issue senior debt securities from time to time, in one or more series under a senior indenture to be entered into between us and a senior trustee to be named in a prospectus supplement, which we refer to as the senior trustee. We may issue subordinated debt securities from time to time, in one or more series under a subordinated indenture to be entered into between us and a subordinated trustee to be named in a prospectus supplement, which we refer to as the subordinated trustee. The forms of senior indenture and subordinated indenture are filed as exhibits to the registration statement of which this prospectus forms a part. Together, the senior indenture and the subordinated indenture are referred to as the indentures and, together, the senior trustee and the subordinated trustee are referred to as the trustees. This prospectus briefly outlines some of the provisions of the indentures. The following summary of the material provisions of the indentures is qualified in its entirety by the provisions of the indentures, including definitions of certain terms used in the indentures. Wherever we refer to particular sections or defined terms of the indentures, those sections or defined terms are incorporated by reference in this prospectus or the applicable prospectus supplement. You should review the indentures that are filed as exhibits to the registration statement of which this prospectus forms a part for additional information.

None of the indentures will limit the amount of debt securities that we may issue. The applicable indenture will provide that debt securities may be issued up to an aggregate principal amount authorized from time to time by us and may be payable in any currency or currency unit designated by us or in amounts determined by reference to an index.

General

The senior debt securities will constitute our unsecured and unsubordinated general obligations and will rank pari passu with our other unsecured and unsubordinated obligations. The subordinated debt securities will constitute our unsecured and subordinated general obligations and will be junior in right of payment to our senior indebtedness (including senior debt securities), as described under the heading Certain Terms of the Subordinated Debt Securities Subordination. The debt securities will be structurally subordinated to all existing and future indebtedness and other liabilities of our subsidiary unless such subsidiary expressly guarantees such debt securities.

The debt securities will be our unsecured obligations. Any secured debt or other secured obligations will be effectively senior to the debt securities to the extent of the value of the assets securing such debt or other obligations.

The applicable prospectus supplement and/or free writing prospectus will include any additional or different terms of the debt securities of any series being offered, including the following terms:

- the title and type of the debt securities;

whether the debt securities will be senior or subordinated debt securities, and, with respect to debt securities issued under the subordinated indenture the terms on which they are subordinated;

the aggregate principal amount of the debt securities;

the price or prices at which we will sell the debt securities;

the maturity date or dates of the debt securities and the right, if any, to extend such date or dates;

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the rate or rates, if any, per year, at which the debt securities will bear interest, or the method of determining such rate or rates;

the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the manner of determination of such interest payment dates and the related record dates;

the right, if any, to extend the interest payment periods and the duration of that extension;

the manner of paying principal and interest and the place or places where principal and interest will be payable;

provisions for a sinking fund, purchase fund or other analogous fund, if any;

any redemption dates, prices, obligations and restrictions on the debt securities;

the currency, currencies or currency units in which the debt securities will be denominated and the currency, currencies or currency units in which principal and interest, if any, on the debt securities may be payable;

any conversion or exchange features of the debt securities;

whether and upon what terms the debt securities may be defeased;

any events of default or covenants in addition to or in lieu of those set forth in the indenture;

whether the debt securities will be issued in definitive or global form or in definitive form only upon satisfaction of certain conditions;

whether the debt securities will be guaranteed as to payment or performance;

any special tax implications of the debt securities; and

any other material terms of the debt securities.

When we refer to principal in this section with reference to the debt securities, we are also referring to premium, if any.

We may from time to time, without notice to or the consent of the holders of any series of debt securities, create and issue further debt securities of any such series ranking equally with the debt securities of such series in all respects (or in all respects other than (1) the payment of interest accruing prior to the issue date of such further debt securities or (2) the first payment of interest following the issue date of such further debt securities). Such further debt securities may be consolidated and form a single series with the debt securities of such series and have the same terms as to status, redemption or otherwise as the debt securities of such series.

You may present debt securities for exchange and you may present debt securities for transfer in the manner, at the places and subject to the restrictions set forth in the debt securities and the applicable prospectus supplement. We will provide you those services without charge, although you may have to pay any tax or other governmental charge payable in connection with any exchange or transfer, as set forth in the indenture.

Debt securities may bear interest at a fixed rate or a floating rate. Debt securities bearing no interest or interest at a rate that at the time of issuance is below the prevailing market rate (original issue discount securities) may be sold at a discount below their stated principal amount. U.S. federal income tax considerations applicable to any such discounted debt securities or to certain debt securities issued at par which are treated as having been issued at a discount for U.S. federal income tax purposes will be described in the applicable prospectus supplement.

We may issue debt securities with the principal amount payable on any principal payment date, or the amount of interest payable on any interest payment date, to be determined by reference to one or more currency exchange rates, securities or baskets of securities, commodity prices or indices. You may receive a payment of

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principal on any principal payment date, or a payment of interest on any interest payment date, that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending on the value on such dates of the applicable currency, security or basket of securities, commodity or index. Information as to the methods for determining the amount of principal or interest payable on any date, the currencies, securities or baskets of securities, commodities or indices to which the amount payable on such date is linked and certain related tax considerations will be set forth in the applicable prospectus supplement.

Certain Terms of the Senior Debt Securities

Covenants. Unless we indicate otherwise in a prospectus supplement, the senior debt securities will not contain any financial or restrictive covenants, including covenants restricting either us or our subsidiary from incurring, issuing, assuming or guaranteeing any indebtedness secured by a lien on any of our or our subsidiary s property or capital stock, or restricting either us or our subsidiary from entering into sale and leaseback transactions.

Consolidation, Merger and Sale of Assets. Unless we indicate otherwise in a prospectus supplement, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to any person, in either case, unless:

- the successor entity, if any, is a U.S. corporation, limited liability company, partnership or trust (subject to certain exceptions provided for in the senior indenture);
- the successor entity assumes our obligations on the senior debt securities and under the senior indenture;
- immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
- certain other conditions are met.

No Protection in the Event of a Change in Control. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the senior debt securities will not contain any provisions that may afford holders of the senior debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control).

Events of Default. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the following are events of default under the senior indenture for any series of senior debt securities:

- failure to pay interest on any senior debt securities of such series when due and payable, if that default continues for a period of 30 days (or such other period as may be specified for such series);
- failure to pay principal on the senior debt securities of such series when due and payable whether at maturity, upon redemption, by declaration or otherwise (and, if specified for such series, the continuance of such

failure for a specified period);

default in the performance of or breach of any of our covenants or agreements in the senior indenture applicable to senior debt securities of such series, other than a covenant breach which is specifically dealt with elsewhere in the senior indenture, and that default or breach continues for a period of 90 days after we receive written notice from the trustee or from the holders of 25% or more in aggregate principal amount of the senior debt securities of such series;

certain events of bankruptcy or insolvency, whether or not voluntary; and

any other event of default provided for in such series of senior debt securities as may be specified in the applicable prospectus supplement.

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The default by us under any other debt, including any other series of debt securities, is not a default under the senior indenture.

If an event of default other than an event of default specified in the fourth bullet point above occurs with respect to a series of senior debt securities and is continuing under the senior indenture, then, and in each such case, either the trustee or the holders of not less than 25% in aggregate principal amount of such series then outstanding under the senior indenture (each such series voting as a separate class) by written notice to us and to the trustee, if such notice is given by the holders, may, and the trustee at the request of such holders shall, declare the principal amount of and accrued interest on such series of senior debt securities to be immediately due and payable, and upon this declaration, the same shall become immediately due and payable.

If an event of default specified in the fourth bullet point above occurs and is continuing, the entire principal amount of and accrued interest on each series of senior debt securities then outstanding shall become immediately due and payable.

Unless otherwise specified in the prospectus supplement relating to a series of senior debt securities originally issued at a discount, the amount due upon acceleration shall include only the original issue price of the senior debt securities, the amount of original issue discount accrued to the date of acceleration and accrued interest, if any.

Upon certain conditions, declarations of acceleration may be rescinded and annulled and past defaults may be waived by the holders of a majority in aggregate principal amount of all the senior debt securities of such series affected by the default, each series voting as a separate class. Furthermore, subject to various provisions in the senior indenture, the holders of a majority in aggregate principal amount of a series of senior debt securities, by notice to the trustee, may waive an existing default or event of default with respect to such senior debt securities and its consequences, except a default in the payment of principal of or interest on such senior debt securities or in respect of a covenant or provision of the senior indenture which cannot be modified or amended without the consent of the holders of each such senior debt security. Upon any such waiver, such default shall cease to exist, and any event of default with respect to such senior debt securities shall be deemed to have been cured, for every purpose of the senior indenture; but no such waiver shall extend to any subsequent or other default or event of default or impair any right consequent thereto.

The holders of a majority in aggregate principal amount of a series of senior debt securities may direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to such senior debt securities. However, the trustee may refuse to follow any direction that conflicts with law or the senior indenture, that may involve the trustee in personal liability or that the trustee determines in good faith may be unduly prejudicial to the rights of holders of such series of senior debt securities not joining in the giving of such direction and may take any other action it deems proper that is not inconsistent with any such direction received from holders of such series of senior debt securities. A holder may not pursue any remedy with respect to the senior indenture or any series of senior debt securities unless:

- the holder gives the trustee written notice of a continuing event of default;

- the holders of at least 25% in aggregate principal amount of such series of senior debt securities make a written request to the trustee to pursue the remedy in respect of such event of default;

the requesting holder or holders offer the trustee indemnity satisfactory to the trustee against any costs, liability or expense;

the trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and

during such 60-day period, the holders of a majority in aggregate principal amount of such series of senior debt securities do not give the trustee a direction that is inconsistent with the request.

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These limitations, however, do not apply to the right of any holder of a senior debt security to receive payment of the principal of and interest on such senior debt security in accordance with the terms of such debt security, or to bring suit for the enforcement of any such payment in accordance with the terms of such debt security, on or after the due date for the senior debt securities, which right shall not be impaired or affected without the consent of the holder.

The senior indenture requires certain of our officers to certify, on or before a fixed date in each year in which any senior debt security is outstanding, as to their knowledge of our compliance with all covenants, agreements and conditions under the senior indenture.

Satisfaction and Discharge. We can satisfy and discharge our obligations to holders of any series of debt securities if:

- we pay or cause to be paid, as and when due and payable, the principal of and any interest on all senior debt securities of such series outstanding under the senior indenture; or

- all senior debt securities of such series have become due and payable or will become due and payable within one year (or are to be called for redemption within one year) and we deposit in trust a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us. Purchasers of the debt securities should consult their own advisers with respect to the tax consequences to them of such deposit and discharge, including the applicability and effect of tax laws other than the U.S. federal income tax law.

Defeasance. Unless the applicable prospectus supplement provides otherwise, the following discussion of legal defeasance and discharge and covenant defeasance will apply to any series of debt securities issued under the indentures.

Legal Defeasance. We can legally release ourselves from any payment or other obligations on the debt securities of any series (called legal defeasance) if certain conditions are met, including the following:

- We deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

- There is a change in current U.S. federal income tax law or an IRS ruling that lets us make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due. Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us.

We deliver to the trustee a legal opinion of our counsel confirming the tax law change or ruling described above.

If we accomplish legal defeasance, as described above, you would have to rely solely on the trust deposit for repayment of the debt securities. You could not look to us for repayment in the event of any shortfall.

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Covenant Defeasance. Without any change of current U.S. federal tax law, we can make the same type of deposit described above and be released from some of the covenants in the debt securities (called covenant defeasance). In that event, you would lose the protection of those covenants but would gain the protection of having money and securities set aside in trust to repay the debt securities. In order to achieve covenant defeasance, we must do the following (among other things):

We must deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

We must deliver to the trustee a legal opinion of our counsel confirming that under current U.S. federal income tax law we may make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due.

If we accomplish covenant defeasance, you could still look to us for repayment of the debt securities if there were a shortfall in the trust deposit. In fact, if one of the events of default occurred (such as our bankruptcy) and the debt securities become immediately due and payable, there may be such a shortfall. Depending on the events causing the default, you may not be able to obtain payment of the shortfall.

Modification and Waiver. We and the trustee may amend or supplement the senior indenture or the senior debt securities without the consent of any holder:

to convey, transfer, assign, mortgage or pledge any assets as security for the senior debt securities of one or more series;

to evidence the succession of a corporation, limited liability company, partnership or trust to us, and the assumption by such successor of our covenants, agreements and obligations under the senior indenture or to otherwise comply with the covenant relating to mergers, consolidations and sales of assets;

to comply with requirements of the SEC in order to effect or maintain the qualification of the senior indenture under the Trust Indenture Act of 1939, as amended;

to add to our covenants such new covenants, restrictions, conditions or provisions for the protection of the holders, and to make the occurrence, or the occurrence and continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default;

to cure any ambiguity, defect or inconsistency in the senior indenture or in any supplemental indenture or to conform the senior indenture or the senior debt securities to the description of senior debt securities of such series set forth in this prospectus or any applicable prospectus supplement;

to provide for or add guarantors with respect to the senior debt securities of any series;

to establish the form or forms or terms of the senior debt securities as permitted by the senior indenture;

to evidence and provide for the acceptance of appointment under the senior indenture by a successor trustee, or to make such changes as shall be necessary to provide for or facilitate the administration of the trusts in the senior indenture by more than one trustee;

to add to, delete from or revise the conditions, limitations and restrictions on the authorized amount, terms, purposes of issue, authentication and delivery of any series of senior debt securities;

to make any change to the senior debt securities of any series so long as no senior debt securities of such series are outstanding; or

to make any change that does not adversely affect the rights of any holder in any material respect.

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Other amendments and modifications of the senior indenture or the senior debt securities issued may be made, and our compliance with any provision of the senior indenture with respect to any series of senior debt securities may be waived, with the consent of the holders of a majority of the aggregate principal amount of the outstanding senior debt securities of all series affected by the amendment or modification (voting together as a single class); provided, however, that each affected holder must consent to any modification, amendment or waiver that:

- extends the final maturity of any senior debt securities of such series;
- reduces the principal amount of any senior debt securities of such series;
- reduces the rate or extends the time of payment of interest on any senior debt securities of such series;
- reduces the amount payable upon the redemption of any senior debt securities of such series;
- changes the currency of payment of principal of or interest on any senior debt securities of such series;
- reduces the principal amount of original issue discount securities payable upon acceleration of maturity or the amount provable in bankruptcy;
- waives an uncured default in the payment of principal of or interest on the senior debt securities (except in the case of a rescission of acceleration as described above);
- changes the provisions relating to the waiver of past defaults or changes or impairs the right of holders to receive payment or to institute suit for the enforcement of any payment or conversion of any senior debt securities of such series on or after the due date therefor;
- modifies any of the provisions of these restrictions on amendments and modifications, except to increase any required percentage or to provide that certain other provisions cannot be modified or waived without the consent of the holder of each senior debt security of such series affected by the modification; or
- reduces the above-stated percentage of outstanding senior debt securities of such series whose holders must consent to a supplemental indenture or modifies or amends or waives certain provisions of or defaults under the senior indenture.

It shall not be necessary for the holders to approve the particular form of any proposed amendment, supplement or waiver, but it shall be sufficient if the holders consent approves the substance thereof. After an amendment, supplement or waiver of the senior indenture in accordance with the provisions described in this section becomes effective, the trustee must give to the holders affected thereby certain notice briefly describing the amendment,

supplement or waiver. Any failure by the trustee to give such notice, or any defect therein, shall not, however, in any way impair or affect the validity of any such amendment, supplemental indenture or waiver.

No Personal Liability of Incorporators, Stockholders, Officers, Directors. The senior indenture provides that no recourse shall be had under any obligation, covenant or agreement of ours in the senior indenture or any supplemental indenture, or in any of the senior debt securities or because of the creation of any indebtedness represented thereby, against any of our incorporators, stockholders, officers or directors, past, present or future, or of any predecessor or successor entity thereof under any law, statute or constitutional provision or by the enforcement of any assessment or by any legal or equitable proceeding or otherwise. Each holder, by accepting the senior debt securities, waives and releases all such liability.

Concerning the Trustee. The senior indenture provides that, except during the continuance of an event of default, the trustee will not be liable except for the performance of such duties as are specifically set forth in the senior indenture. If an event of default has occurred and is continuing, the trustee will exercise such rights and powers vested in it under the senior indenture and will use the same degree of care and skill in its exercise as a prudent person would exercise under the circumstances in the conduct of such person s own affairs.

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The senior indenture and the provisions of the Trust Indenture Act of 1939 incorporated by reference therein contain limitations on the rights of the trustee thereunder, should it become a creditor of ours or our subsidiary, to obtain payment of claims in certain cases or to realize on certain property received by it in respect of any such claims, as security or otherwise. The trustee is permitted to engage in other transactions, provided that if it acquires any conflicting interest (as defined in the Trust Indenture Act), it must eliminate such conflict or resign.

We may have normal banking relationships with the senior trustee in the ordinary course of business.

Unclaimed Funds. All funds deposited with the trustee or any paying agent for the payment of principal, premium, interest or additional amounts in respect of the senior debt securities that remain unclaimed for two years after the date upon which such principal, premium or interest became due and payable will be repaid to us. Thereafter, any right of any holder of senior debt securities to such funds shall be enforceable only against us, and the trustee and paying agents will have no liability therefor.

Governing Law. The senior indenture and the senior debt securities will be governed by, and construed in accordance with, the internal laws of the State of New York.

Certain Terms of the Subordinated Debt Securities

Other than the terms of the subordinated indenture and subordinated debt securities relating to subordination or otherwise as described in the prospectus supplement relating to a particular series of subordinated debt securities, the terms of the subordinated indenture and subordinated debt securities are identical in all material respects to the terms of the senior indenture and senior debt securities.

Additional or different subordination terms may be specified in the prospectus supplement applicable to a particular series.

Subordination. The indebtedness evidenced by the subordinated debt securities is subordinate to the prior payment in full of all of our senior indebtedness, as defined in the subordinated indenture. During the continuance beyond any applicable grace period of any default in the payment of principal, premium, interest or any other payment due on any of our senior indebtedness, we may not make any payment of principal of or interest on the subordinated debt securities (except for certain sinking fund payments). In addition, upon any payment or distribution of our assets upon any dissolution, winding-up, liquidation or reorganization, the payment of the principal of and interest on the subordinated debt securities will be subordinated to the extent provided in the subordinated indenture in right of payment to the prior payment in full of all our senior indebtedness. Because of this subordination, if we dissolve or otherwise liquidate, holders of our subordinated debt securities may receive less, ratably, than holders of our senior indebtedness. The subordination provisions do not prevent the occurrence of an event of default under the subordinated indenture.

The term senior indebtedness of a person means with respect to such person the principal of, premium, if any, interest on, and any other payment due pursuant to any of the following, whether outstanding on the date of the subordinated indenture or incurred by that person in the future:

all of the indebtedness of that person for money borrowed;

all of the indebtedness of that person evidenced by notes, debentures, bonds or other securities sold by that person for money;

all of the lease obligations that are capitalized on the books of that person in accordance with generally accepted accounting principles;

all indebtedness of others of the kinds described in the first two bullet points above and all lease obligations of others of the kind described in the third bullet point above that the person, in any manner, assumes or guarantees or that the person in effect guarantees through an agreement to purchase, whether that agreement is contingent or otherwise; and

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all renewals, extensions or refundings of indebtedness of the kinds described in the first, second or fourth bullet point above and all renewals or extensions of leases of the kinds described in the third or fourth bullet point above;

unless, in the case of any particular indebtedness, renewal, extension or refunding, the instrument creating or evidencing it or the assumption or guarantee relating to it expressly provides that such indebtedness, renewal, extension or refunding is not superior in right of payment to the subordinated debt securities. Our senior debt securities constitute senior indebtedness for purposes of the subordinated debt indenture.

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DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our restated certificate of incorporation, our by-laws and applicable provisions of Delaware corporate law. You should read our restated certificate of incorporation and by-laws, which are filed as exhibits to the registration statement of which this prospectus forms a part, for the provisions that are important to you.

Our authorized capital stock consists of 125,000,000 shares of common stock, par value $0.0001 per share, and 5,000,000 shares of preferred stock, par value $0.0001 per share. As of May 5, 2014, 33,154,689 shares of common stock were outstanding and no shares of preferred stock were outstanding.

Common Stock

Voting Rights. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our restated certificate of incorporation and bylaws also provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described below under Provisions of Our Restated Certificate of Incorporation and By-laws and Delaware Law That May Have Anti-Takeover Effects Removal of Directors and Stockholder Action by Written Consent; Special Meetings.

Dividends. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of any outstanding preferred stock.

Liquidation and Dissolution. In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock.

Other Rights. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Transfer Agent and Registrar. Computershare Trust Company, Inc. is the transfer agent and registrar for our common stock.

Listing on The NASDAQ Global Market. Our common stock is listed on The NASDAQ Global Market under the symbol EPZM .

Preferred Stock

We are authorized to issue blank check preferred stock, which may be issued in one or more series upon authorization of our board of directors. Our board of directors is authorized to fix the designation of the series, the number of

authorized shares of the series, dividend rights and terms, conversion rights, voting rights, redemption rights and terms, liquidation preferences and any other rights, powers, preferences and limitations

applicable to each series of preferred stock. The authorized shares of our preferred stock are available for issuance without further action by our stockholders, unless such action is required by applicable law or the rules of any stock exchange on which our securities may be listed. If the approval of our stockholders is not required for the issuance of shares of our preferred stock, our board may determine not to seek stockholder approval. The specific terms of any series of preferred stock offered pursuant to this prospectus will be described in the prospectus supplement relating to that series of preferred stock.

A series of our preferred stock could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make any determination to issue preferred shares based upon its judgment as to the best interests of our stockholders. Our directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock.

The preferred stock has the terms described below unless otherwise provided in the prospectus supplement relating to a particular series of preferred stock. You should read the prospectus supplement relating to the particular series of preferred stock being offered for specific terms, including:

- the designation and stated value per share of the preferred stock and the number of shares offered;
- the amount of liquidation preference per share;
- the price at which the preferred stock will be issued;
- the dividend rate, or method of calculation of dividends, the dates on which dividends will be payable, whether dividends will be cumulative or noncumulative and, if cumulative, the dates from which dividends will commence to accumulate;
- any redemption or sinking fund provisions;
- if other than the currency of the United States, the currency or currencies including composite currencies in which the preferred stock is denominated and/or in which payments will or may be payable;
- any conversion provisions; and
- any other rights, preferences, privileges, limitations and restrictions on the preferred stock.

The preferred stock will, when issued, be fully paid and non-assessable. Unless otherwise specified in the prospectus supplement, each series of preferred stock will rank equally as to dividends and liquidation rights in all respects with

each other series of preferred stock. The rights of holders of shares of each series of preferred stock will be subordinate to those of our general creditors.

Rank. Unless otherwise specified in the prospectus supplement, the preferred stock will, with respect to dividend rights and rights upon our liquidation, dissolution or winding up of our affairs, rank:

senior to our common stock and to all equity securities ranking junior to such preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs;

on a parity with all equity securities issued by us, the terms of which specifically provide that such equity securities rank on a parity with the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs; and

junior to all equity securities issued by us, the terms of which specifically provide that such equity securities rank senior to the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs.

The term equity securities does not include convertible debt securities.

Dividends. Holders of the preferred stock of each series will be entitled to receive, when, as and if declared by our board of directors, cash dividends at such rates and on such dates described in the prospectus supplement. Different series of preferred stock may be entitled to dividends at different rates or based on different methods of calculation. The dividend rate may be fixed or variable or both. Dividends will be payable to the holders of record as they appear on our stock books on record dates fixed by our board of directors, as specified in the applicable prospectus supplement.

Dividends on any series of preferred stock may be cumulative or noncumulative, as described in the applicable prospectus supplement. If our board of directors does not declare a dividend payable on a dividend payment date on any series of noncumulative preferred stock, then the holders of that noncumulative preferred stock will have no right to receive a dividend for that dividend payment date, and we will have no obligation to pay the dividend accrued for that period, whether or not dividends on that series are declared payable on any future dividend payment dates. Dividends on any series of cumulative preferred stock will accrue from the date we initially issue shares of such series or such other date specified in the applicable prospectus supplement.

No dividends may be declared or paid or funds set apart for the payment of any dividends on any parity securities unless full dividends have been paid or set apart for payment on the preferred stock. If full dividends are not paid, the preferred stock will share dividends pro rata with the parity securities.

No dividends may be declared or paid or funds set apart for the payment of dividends on any junior securities unless full dividends for all dividend periods terminating on or prior to the date of the declaration or payment will have been paid or declared and a sum sufficient for the payment set apart for payment on the preferred stock.

Liquidation Preference. Upon any voluntary or involuntary liquidation, dissolution or winding up of our affairs, then, before we make any distribution or payment to the holders of any common stock or any other class or series of our capital stock ranking junior to the preferred stock in the distribution of assets upon any liquidation, dissolution or winding up of our affairs, the holders of each series of preferred stock shall be entitled to receive out of assets legally available for distribution to stockholders, liquidating distributions in the amount of the liquidation preference per share set forth in the prospectus supplement, plus any accrued and unpaid dividends thereon. Such dividends will not include any accumulation in respect of unpaid noncumulative dividends for prior dividend periods. Unless otherwise specified in the prospectus supplement, after payment of the full amount of their liquidating distributions, the holders of preferred stock will have no right or claim to any of our remaining assets. Upon any such voluntary or involuntary liquidation, dissolution or winding up, if our available assets are insufficient to pay the amount of the liquidating distributions on all outstanding preferred stock and the corresponding amounts payable on all other classes or series of our capital stock ranking on parity with the preferred stock and all other such classes or series of shares of capital stock ranking on parity with the preferred stock in the distribution of assets, then the holders of the preferred stock and all other such classes or series of capital stock will share ratably in any such distribution of assets in proportion to the full liquidating distributions to which they would otherwise be entitled.

Upon any such liquidation, dissolution or winding up and if we have made liquidating distributions in full to all holders of preferred stock, we will distribute our remaining assets among the holders of any other classes or series of capital stock ranking junior to the preferred stock according to their respective rights and preferences and, in each case, according to their respective number of shares. For such purposes, our consolidation or merger with or into any other corporation, trust or entity, or the sale, lease or conveyance of all or substantially all of our property or assets will not be deemed to constitute a liquidation, dissolution or winding up of our affairs.

Redemption. If so provided in the applicable prospectus supplement, the preferred stock will be subject to mandatory redemption or redemption at our option, as a whole or in part, in each case upon the terms, at the times and at the redemption prices set forth in such prospectus supplement.

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The prospectus supplement relating to a series of preferred stock that is subject to mandatory redemption will specify the number of shares of preferred stock that shall be redeemed by us in each year commencing after a date to be specified, at a redemption price per share to be specified, together with an amount equal to all accrued and unpaid dividends thereon to the date of redemption. Unless the shares have a cumulative dividend, such accrued dividends will not include any accumulation in respect of unpaid dividends for prior dividend periods. We may pay the redemption price in cash or other property, as specified in the applicable prospectus supplement. If the redemption price for preferred stock of any series is payable only from the net proceeds of the issuance of shares of our capital stock, the terms of such preferred stock may provide that, if no such shares of our capital stock shall have been issued or to the extent the net proceeds from any issuance are insufficient to pay in full the aggregate redemption price then due, such preferred stock shall automatically and mandatorily be converted into the applicable shares of our capital stock pursuant to conversion provisions specified in the applicable prospectus supplement. Notwithstanding the foregoing, we will not redeem any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on the preferred stock for all past dividend periods and the then current dividend period; or

- if such series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends for the then current dividend period.

In addition, we will not acquire any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on all outstanding shares of such series of preferred stock for all past dividend periods and the then current dividend period; or

- if that series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends on the preferred stock of such series for the then current dividend period.

However, at any time we may purchase or acquire preferred stock of that series (1) pursuant to a purchase or exchange offer made on the same terms to holders of all outstanding preferred stock of such series or (2) by conversion into or exchange for shares of our capital stock ranking junior to the preferred stock of such series as to dividends and upon liquidation.

If fewer than all of the outstanding shares of preferred stock of any series are to be redeemed, we will determine the number of shares that may be redeemed pro rata from the holders of record of such shares in proportion to the number of such shares held or for which redemption is requested by such holder or by any other equitable manner that we determine. Such determination will reflect adjustments to avoid redemption of fractional shares.

Unless otherwise specified in the prospectus supplement, we will mail notice of redemption at least 30 days but not more than 60 days before the redemption date to each holder of record of preferred stock to be redeemed at the address shown on our stock transfer books. Each notice shall state:

the redemption date;

the number of shares and series of preferred stock to be redeemed;

the redemption price;

the place or places where certificates for such preferred stock are to be surrendered for payment of the redemption price;

that dividends on the shares to be redeemed will cease to accrue on such redemption date;

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the date on which the holder s conversion rights, if any, as to such shares shall terminate; and

the specific number of shares to be redeemed from each such holder if fewer than all the shares of any series are to be redeemed.

If notice of redemption has been given and we have set aside the funds necessary for such redemption in trust for the benefit of the holders of any shares called for redemption, then from and after the redemption date, dividends will cease to accrue on such shares, and all rights of the holders of such shares will terminate, except the right to receive the redemption price.

Voting Rights. Holders of preferred stock will not have any voting rights, except as required by law or as indicated in the applicable prospectus supplement.

Unless otherwise provided for under the terms of any series of preferred stock, no consent or vote of the holders of shares of preferred stock or any series thereof shall be required for any amendment to our restated certificate of incorporation that would increase the number of authorized shares of preferred stock or the number of authorized shares of any series thereof or decrease the number of authorized shares of preferred stock or the number of authorized shares of any series thereof (but not below the number of authorized shares of preferred stock or such series, as the case may be, then outstanding).

Conversion Rights. The terms and conditions, if any, upon which any series of preferred stock is convertible into our common stock will be set forth in the applicable prospectus supplement relating thereto. Such terms will include the number of shares of common stock into which the shares of preferred stock are convertible, the conversion price, rate or manner of calculation thereof, the conversion period, provisions as to whether conversion will be at our option or at the option of the holders of the preferred stock, the events requiring an adjustment of the conversion price and provisions affecting conversion in the event of the redemption.

Transfer Agent and Registrar. The transfer agent and registrar for the preferred stock will be set forth in the applicable prospectus supplement.

Provisions of Our Restated Certificate of Incorporation and By-laws and Delaware Law That May Have Anti-Takeover Effects

Delaware law contains, and our restated certificate of incorporation and our bylaws contain, provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Removal of Directors. A director may be removed only for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office.

Stockholder Action by Written Consent; Special Meetings. Our restated certificate of incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such holders and may not be effected by any consent in writing by such holders. Our restated certificate of incorporation and bylaws also provide that, except as otherwise required by law, special meetings of our stockholders

can only be called by our chairman of the board, our chief executive officer or our board of directors.

Advance Notice Requirements for Stockholder Proposals. Our bylaws have established an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed

nominations of persons for election to our board of directors. Stockholders at an annual meeting will only be able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder s intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities.

Delaware Business Combination Statute. We are subject to Section 203 of the Delaware General Corporation Law. Subject to specified exceptions, Section 203 of the Delaware General Corporation Law restricts some types of transactions and business combinations between a corporation and a 15% stockholder. A 15% stockholder is generally considered by Section 203 to be a person owning 15% or more of the corporation s outstanding voting stock. Section 203 refers to a 15% stockholder as an interested stockholder. Section 203 restricts these transactions for a period of three years from the date the stockholder acquires 15% or more of our outstanding voting stock. With some exceptions, unless the transaction is approved by the board of directors and the holders of at least two-thirds of the outstanding voting stock of the corporation, Section 203 prohibits significant business transactions such as:

- a merger with, disposition of significant assets to or receipt of disproportionate financial benefits by the interested stockholder, and
- any other transaction that would increase the interested stockholder s proportionate ownership of any class or series of our capital stock.

The shares held by the interested stockholder are not counted as outstanding when calculating the two-thirds of the outstanding voting stock needed for approval.

The prohibition against these transactions does not apply if:

- prior to the time that any stockholder became an interested stockholder, the board of directors approved either the business combination or the transaction in which such stockholder acquired 15% or more of our outstanding voting stock, or
- the interested stockholder owns at least 85% of our outstanding voting stock as a result of a transaction in which such stockholder acquired 15% or more of our outstanding voting stock. Shares held by persons who are both directors and officers or by some types of employee stock plans are not counted as outstanding when making this calculation.

Amendment of Restated Certificate of Incorporation and Bylaws. The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation s restated certificate of incorporation or bylaws, unless a corporation s restated certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of

directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described above under Removal of Directors and Stockholder Action by Written Consent; Special Meetings.

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DESCRIPTION OF UNITS

We may issue units comprised of one or more of the other securities that may be offered under this prospectus, in any combination. The following, together with the additional information we may include in the applicable prospectus supplement, summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms summarized below will apply generally to any units we may offer, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement.

Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately at any time, or at any time before a specified date.

Any applicable prospectus supplement will describe:

- the material terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any material provisions relating to the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units; and
- any material provisions of the governing unit agreement that differ from those described above.

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DESCRIPTION OF WARRANTS

We may issue warrants to purchase common stock, preferred stock or debt securities. We may offer warrants separately or together with one or more additional warrants, common stock, preferred stock or debt securities, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

- the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants are to be sold separately or with other securities as parts of units;
- whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- the designation and terms of any equity securities purchasable upon exercise of the warrants;
- the designation, aggregate principal amount, currency and terms of any debt securities that may be purchased upon exercise of the warrants;

if applicable, the designation and terms of the preferred stock with which the warrants are issued and the number of warrants issued with each security;

if applicable, the date from and after which any warrants issued as part of a unit and the related debt securities, preferred stock or common stock will be separately transferable;

the number of shares of common stock or preferred stock purchasable upon exercise of a warrant and the price at which those shares may be purchased;

if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;

information with respect to book-entry procedures, if any;

the anti-dilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;

any redemption or call provisions; and

any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

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FORMS OF SECURITIES

Each debt security, unit and warrant will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless the applicable prospectus supplement provides otherwise, certificated securities in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depositary or its nominee as the owner of the debt securities, units or warrants represented by these global securities. The depositary maintains a computerized system that will reflect each investor s beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

Global Securities

We may issue the debt securities, units and warrants in the form of one or more fully registered global securities that will be deposited with a depositary or its nominee identified in the applicable prospectus supplement and registered in the name of that depositary or nominee. In those cases, one or more global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal or face amount of the securities to be represented by global securities. Unless and until it is exchanged in whole for securities in definitive registered form, a global security may not be transferred except as a whole by and among the depositary for the global security, the nominees of the depositary or any successors of the depositary or those nominees.

If not described below, any specific terms of the depositary arrangement with respect to any securities to be represented by a global security will be described in the prospectus supplement relating to those securities. We anticipate that the following provisions will apply to all depositary arrangements.

Ownership of beneficial interests in a global security will be limited to persons, called participants, that have accounts with the depositary or persons that may hold interests through participants. Upon the issuance of a global security, the depositary will credit, on its book-entry registration and transfer system, the participants accounts with the respective principal or face amounts of the securities beneficially owned by the participants. Any dealers, underwriters or agents participating in the distribution of the securities will designate the accounts to be credited. Ownership of beneficial interests in a global security will be shown on, and the transfer of ownership interests will be effected only through, records maintained by the depositary, with respect to interests of participants, and on the records of participants, with respect to interests of persons holding through participants. The laws of some states may require that some purchasers of securities take physical delivery of these securities in definitive form. These laws may impair your ability to own, transfer or pledge beneficial interests in global securities.

So long as the depositary, or its nominee, is the registered owner of a global security, that depositary or its nominee, as the case may be, will be considered the sole owner or holder of the securities represented by the global security for all purposes under the applicable indenture or warrant agreement. Except as described below, owners of beneficial interests in a global security will not be entitled to have the securities represented by the global security registered in their names, will not receive or be entitled to receive physical delivery of the securities in definitive form and will not be considered the owners or holders of the securities under the applicable indenture or warrant agreement. Accordingly, each person owning a beneficial interest in a global security must rely on the procedures of the depositary for that global security and, if that person is not a participant, on the procedures of the participant through which the person owns its interest, to exercise any rights of a holder under the applicable indenture or warrant agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of

a beneficial interest in a global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture or warrant agreement, the depositary for the global security would authorize the participants holding the relevant beneficial

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interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to warrants or units, represented by a global security registered in the name of a depositary or its nominee will be made to the depositary or its nominee, as the case may be, as the registered owner of the global security. None of us, or any trustee, warrant agent, unit agent or other agent of ours, or any agent of any trustee, warrant agent or unit agent will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

We expect that the depositary for any of the securities represented by a global security, upon receipt of any payment to holders of principal, premium, interest or other distribution of underlying securities or other property on that registered global security, will immediately credit participants accounts in amounts proportionate to their respective beneficial interests in that global security as shown on the records of the depositary. We also expect that payments by participants to owners of beneficial interests in a global security held through participants will be governed by standing customer instructions and customary practices, as is now the case with the securities held for the accounts of customers or registered in street name, and will be the responsibility of those participants.

If the depositary for any of the securities represented by a global security is at any time unwilling or unable to continue as depositary or ceases to be a clearing agency registered under the Exchange Act, and a successor depositary registered as a clearing agency under the Exchange Act is not appointed by us within 90 days, we will issue securities in definitive form in exchange for the global security that had been held by the depositary. Any securities issued in definitive form in exchange for a global security will be registered in the name or names that the depositary gives to the relevant trustee, warrant agent, unit agent or other relevant agent of ours or theirs. It is expected that the depositary s instructions will be based upon directions received by the depositary from participants with respect to ownership of beneficial interests in the global security that had been held by the depositary.

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PLAN OF DISTRIBUTION

We may sell securities:

through underwriters;

through dealers;

through agents;

directly to purchasers; or

through a combination of any of these methods of sale.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. We will, in the prospectus supplement relating to such offering, name any agent that could be viewed as an underwriter under the Securities Act, and describe any commissions that we must pay. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

The distribution of the securities may be effected from time to time in one or more transactions:

at a fixed price, or prices, which may be changed from time to time;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

the name of the agent or any underwriters;

the public offering or purchase price and the proceeds we will receive from the sale of the securities;

any discounts and commissions to be allowed or re-allowed or paid to the agent or underwriters;

all other items constituting underwriting compensation;

any discounts and commissions to be allowed or re-allowed or paid to dealers; and

any exchanges on which the securities will be listed.

If any underwriters or agents are utilized in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

If a dealer is utilized in the sale of the securities in respect of which this prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

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If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Remarketing firms, agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and

- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Certain agents, underwriters and dealers, and their associates and affiliates may be customers of, have borrowing relationships with, engage in other transactions with, and/or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallot in connection with the offering, creating a short position for their own accounts. In addition, to cover overallotments or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in three business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than three scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the third

business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle more than three scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

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The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

In compliance with the guidelines of the Financial Industry Regulatory Authority, or FINRA, the aggregate maximum discount, commission or agency fees or other items constituting underwriting compensation to be received by any FINRA member or independent broker-dealer will not exceed 8% of the proceeds from any offering pursuant to this prospectus and any applicable prospectus supplement.

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LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Wilmer Cutler Pickering Hale and Dorr LLP.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2013, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP s report, given on their authority as experts in accounting and auditing.

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6,000,000 Shares

Epizyme, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Leerink Partners | **Cowen and Company** | **RBC Capital Markets**

Lead Manager

JMP Securities

Co-Managers

SunTrust Robinson Humphrey | **Mizuho Securities**

March 17, 2015