

Epizyme, Inc.
Form 424B5
March 07, 2019
Table of Contents

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered(1)	Proposed maximum offering price per unit	Proposed maximum aggregate offering price(1)	Amount of registration fee(2)
Common Stock, par value \$0.0001 per share	11,500,000	\$11.50	\$132,250,000	\$16,028.70

- (1) Assumes exercise in full of the underwriters' option to purchase up to 1,500,000 additional shares of Common Stock.
- (2) Calculated in accordance with Rule 457(r) under the Securities Act of 1933, as amended. This Calculation of Registration Fee table shall be deemed to update the Calculation of Registration Fee table in the registrant's Registration Statement on Form S-3 (File No. 333-224159) in accordance with Rules 456(b) and 457(r) under the Securities Act of 1933, as amended.

Table of Contents

Filed pursuant to Rule 424(b)(5)
Registration File No. 333-224159

Prospectus Supplement

(To Prospectus Dated April 5, 2018)

10,000,000 Shares

Epizyme, Inc.

Common Stock

\$11.50 Per Share

We are offering 10,000,000 shares of our common stock. Our common stock is listed on The Nasdaq Global Select Market under the symbol EPZM. The last reported sale price of our common stock on The Nasdaq Global Select Market on March 6, 2019 was \$12.03 per share.

Investing in our common stock involves risks. See Risk Factors beginning on page S-7.

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.

Concurrently with this offering of common stock, and pursuant to a separate prospectus supplement, we are also conducting a public offering (the Concurrent Offering) of 304,348 shares of our Series A convertible preferred stock, or the Series A preferred stock (and the shares of common stock issuable from time to time upon conversion of the Series A preferred stock).

	PER SHARE	TOTAL
Public offering price	\$ 11.50	\$ 115,000,000
Underwriting discount ⁽¹⁾	\$ 0.805	\$ 8,050,000
Proceeds, before expenses, to Epizyme, Inc.	\$ 10.695	\$ 106,950,000

(1) We refer you to **Underwriting** beginning on page S-16 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 an additional 1,500,000 shares of our common stock. See **Underwriting** for more information.

The underwriters expect to deliver the shares to purchasers on or about March 11, 2019.

Joint Book-Running Managers

Jefferies

Citigroup
Lead Manager

Cowen

Wedbush PacGrow
Co-Manager

H.C. Wainwright & Co.
Prospectus Supplement dated March 6, 2019

Table of Contents

TABLE OF CONTENTS

PROSPECTUS SUPPLEMENT

<u>ABOUT THIS PROSPECTUS SUPPLEMENT</u>	S-ii
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	S-iii
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-1
<u>RISK FACTORS</u>	S-7
<u>USE OF PROCEEDS</u>	S-9
<u>DILUTION</u>	S-11
<u>MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF COMMON STOCK</u>	S-12
<u>UNDERWRITING</u>	S-16
<u>LEGAL MATTERS</u>	S-23
<u>EXPERTS</u>	S-24
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	S-25
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	S-26

PROSPECTUS

<u>ABOUT THIS PROSPECTUS</u>	1
Table of Contents	4

<u>WHERE YOU CAN FIND MORE INFORMATION</u>	2
<u>INCORPORATION BY REFERENCE</u>	2
<u>FORWARD-LOOKING STATEMENTS</u>	3
<u>EPIZYME, INC.</u>	4
<u>RISK FACTORS</u>	5
<u>CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES</u>	6
<u>USE OF PROCEEDS</u>	7
<u>DESCRIPTION OF DEBT SECURITIES</u>	8
<u>DESCRIPTION OF CAPITAL STOCK</u>	17
<u>DESCRIPTION OF UNITS</u>	23
<u>DESCRIPTION OF WARRANTS</u>	24
<u>FORMS OF SECURITIES</u>	25
<u>PLAN OF DISTRIBUTION</u>	27
<u>LEGAL MATTERS</u>	29
<u>EXPERTS</u>	29

Table of Contents

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.

S-ii

Table of Contents

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, predict, target, potential, will, would, could, should, continue, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein include, among other things, statements about:

our plans to develop and commercialize novel epigenetic therapies for patients with cancer and other serious diseases;

our ongoing and planned clinical trials, including the timing of initiation and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;

our ability to achieve anticipated milestones under our collaborations;

the timing of and our ability to apply for, 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 expectations related to the use of proceeds for this offering and the Concurrent Offering;

the successful completion of the Concurrent 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 and in the Risk Factors section of our Annual Report on Form 10-K for the year ended December 31, 2018 incorporated herein by reference, 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.

S-iii

Table of Contents

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 herein and therein. 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-7 of this prospectus supplement and in Part I, Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, 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 late-stage biopharmaceutical company that is committed to rewriting treatment for people with cancer and other serious diseases through the discovery, development, and commercialization of novel epigenetic medicines. By focusing on the genetic drivers of disease, our science seeks to match targeted medicines with the patients who need them. We are developing our lead product candidate, tazemetostat, an oral, first-in-class, selective small molecule inhibitor of the EZH2 histone methyltransferase, or HMT, for the treatment of a broad range of cancer types in multiple treatment settings, and developing our novel G9a program, EZM8266, for the treatment of sickle cell disease, or SCD.

We have taken a pipeline in a product approach to developing tazemetostat with a broad clinical development program through company-sponsored studies and collaborations. This program is evaluating tazemetostat as both a monotherapy and combination treatment in hematological malignancies and solid tumors for both late and early lines of treatment. Tazemetostat has shown meaningful clinical activity as a monotherapy in multiple cancer indications and has been generally well-tolerated across clinical trials to date. Based on positive data in our two lead indications, epithelioid sarcoma and follicular lymphoma, or FL, and interactions with the United States Food and Drug Administration, or the FDA, we are planning to submit New Drug Applications, or NDAs, for accelerated approval of tazemetostat for each proposed indication in 2019, subject to the results of our ongoing trials in those indications.

In our hematological malignancy program, we are conducting a multi-cohort, global Phase 2 study evaluating tazemetostat's treatment potential in patients with relapsed or refractory non-Hodgkin lymphoma, or NHL. Two cohorts are evaluating tazemetostat as a monotherapy for patients with relapsed or refractory FL, one of the most prevalent forms of NHL, both with and without EZH2 activating mutations. In December 2018, we completed target enrollment of FL patients in our study, with 54 patients with wild-type EZH2 and 45 patients with EZH2 activating mutations. Based on interactions with the FDA, we believe we have identified a path to submission for accelerated approval of tazemetostat in FL patients with either an EZH2 activating mutation or wild-type EZH2, whose disease has progressed following two or more lines of therapy. We are targeting submission of an NDA for accelerated approval for tazemetostat for FL in this population in the fourth quarter of 2019, subject to the results of our ongoing trial in this indication.

As part of an accelerated approval strategy, we will need to conduct a confirmatory clinical program to verify clinical benefit and support the full approval of tazemetostat. We intend to review our proposed confirmatory program with the FDA, and to finalize its design in the first half of 2019. We hope to leverage the confirmatory program to expand tazemetostat into the second-line treatment setting for patients with FL, both with and without EZH2 activating mutations. In addition, we plan to evaluate tazemetostat treatment in combination with other therapies. In mid-2019, we anticipate initiating a combination study that would compare tazemetostat plus rituximab and Revlimid, a

chemotherapeutic-free treatment regimen referred to as R2, versus R2 with placebo in patients with relapsed or refractory FL, both with and without EZH2 activating mutations. In addition, we are finalizing plans for a trial of tazemetostat in combination with rituxan for the

S-1

Table of Contents

treatment of patients with relapsed and refractory FL. Based on clinical activity observed with tazemetostat in combination with R-CHOP as a front-line treatment for patients with diffuse large B-cell lymphoma, or DLBCL, we are evaluating the opportunity to investigate this combination as a front-line treatment for patients with FL. In collaboration with The Lymphoma Study Association, or LYSA, we are continuing to evaluate tazemetostat with R-CHOP as a front-line treatment for high-risk patients with DLBCL. In addition, Genentech Inc., or Genentech, is evaluating the combination of tazemetostat with its checkpoint inhibitor, Tecentriq (atezolizumab), for the treatment of patients with relapsed or refractory DLBCL, with preliminary data expected from that study in 2019.

In our solid tumor program, we are evaluating tazemetostat's treatment potential in adults and children with molecularly defined solid tumors, including INI1- and SMARCA4-negative tumors, which we collectively refer to as INI1-negative tumors. We are conducting a multi-cohort global Phase 2 trial of tazemetostat in adults with INI1-negative tumors, including epithelioid sarcoma or chordoma. Based on positive data that we have observed in patients with epithelioid sarcoma in the ongoing Phase 2 study, we are targeting submission of our first NDA for accelerated approval of tazemetostat for the treatment of epithelioid sarcoma in the second quarter of 2019. In connection with this submission, we will need to conduct a confirmatory program to verify clinical benefit and support the full approval of tazemetostat. We plan to explore with the FDA utilizing the natural history study in epithelioid sarcoma that we are conducting to serve as confirmatory evidence required in connection with any accelerated approval. The cohort of patients in the phase 2 study of chordoma patients is ongoing, and we are evaluating tazemetostat in the dose-expansion portion of a Phase 1 study in pediatric patients with INI1-negative tumors, with plans to report updated data in 2019.

We own the global development and commercialization rights to tazemetostat outside of Japan. Eisai Co. Ltd, or Eisai, holds the rights to develop and commercialize tazemetostat in Japan. We intend to build a focused field presence and marketing capabilities to commercialize tazemetostat for the epithelioid sarcoma and follicular lymphoma indications in the United States. We have begun building the infrastructure necessary to support the launch and marketing of tazemetostat for epithelioid sarcoma, and believe we can adequately address this patient population through a modest field force of less than 25 professionals. For geographies outside the United States, we are evaluating the most efficient path to reach patients, including through potential collaborations.

Tazemetostat is covered by claims of U.S. and European composition of matter patents, which are expected to expire in 2032, exclusive of any patent term or other extensions. Tazemetostat has been granted Fast Track designation by the FDA in patients with relapsed or refractory FL, with or without activating EZH2 mutations, relapsed or refractory DLBCL with EZH2 activating mutations and metastatic or locally advanced epithelioid sarcoma who have progressed on or following an anthracycline-based treatment regimen. The FDA has also granted orphan drug designation to tazemetostat for the treatment of patients with FL, malignant rhabdoid tumors, or MRT, soft tissue sarcoma, or STS, and mesothelioma. The orphan drug designation for the treatment of MRT applies to INI1-negative MRT as well as SMARCA4-negative malignant rhabdoid tumor of ovary, or MRTO.

Beyond tazemetostat, we are building an early pipeline to further support our leadership in epigenetics. We are developing our wholly-owned G9a candidate, EZM8266, for the treatment of people with sickle cell disease. We have completed IND-enabling studies for this program and plan to begin clinical evaluation with a safety and dose-finding study in the second half of 2019. In November 2018, we entered a strategic collaboration with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim, focused on the research, development and commercialization of novel small molecule inhibitors, discovered by us, directed toward two previously unaddressed epigenetic targets as potential therapies for people with cancer. Specifically, these targets are enzymes within the helicase and histone acetyltransferase, or HAT, families that when dysregulated have been linked to the development of cancers that currently lack therapeutic options. We also have collaborations with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK, focused on the development of PRMT inhibitors discovered by us, and with Celgene

Corporation and Celgene RIVOT Ltd., an affiliate of

S-2

Table of Contents

Celgene Corporation, which we collectively refer to as Celgene, focused on the development of pinometostat and small molecule inhibitors directed to three HMT targets.

Corporate Strategy

Our goal is to become a biopharmaceutical company developing and commercializing novel epigenetic therapies for people with cancer and other serious diseases. The key elements of our corporate strategy are to:

rapidly advance the clinical development of tazemetostat in solid tumors and hematological malignancies;

collaborate closely with the FDA and other regulatory bodies to pursue the registration of tazemetostat with accelerated approval for epithelioid sarcoma and FL;

expand the treatment utility for tazemetostat through a broad development program evaluating its benefit in different combinations, in both early- and late-lines of treatment and in additional indications;

establish commercialization capabilities in the United States;

utilize our drug discovery platform to build a pipeline of inhibitors against chromatin modifying proteins, or CMPs;

develop diagnostics for use with our therapeutic candidates, where appropriate; and

leverage strategic collaborations that can contribute to our ability to rapidly advance and commercialize our product candidates.

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 and in Part I, Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018. These risks include the following:

We have incurred significant losses since our inception. Our accumulated deficit was \$586.7 million as of December 31, 2018, 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.

Our research and development is focused on the creation of novel epigenetic therapies for patients with cancer and other diseases, 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.

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.

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.

We cannot predict whether or when any of our product candidates will prove effective or safe in clinical trials, if we will be able to participate in any expedited review and approval programs for such product candidates, if we will be able to satisfy the criteria for any path to registration for our product candidates discussed with the FDA, if we will submit applications for approval for our product candidates on a timely basis or at all, and if any of our product candidates will receive regulatory approval on a timely basis or at all.

Table of Contents

If we are required to develop a companion diagnostic and if we or our collaborators 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.

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.

Concurrent Offering of Series A Preferred Stock

Concurrently with this offering of common stock, we are conducting a public offering of 304,348 shares of our Series A preferred stock (and the 3,043,480 shares of common stock issuable from time to time upon conversion of the Series A preferred stock), which we refer to as the Concurrent Offering. The Concurrent Offering is being conducted as a separate public offering by means of a separate prospectus supplement. This offering is not contingent upon the completion of the Concurrent Offering and the Concurrent Offering is not contingent upon the completion of this offering. We cannot assure you that either or both of the offerings will be completed.

Table of Contents

THE OFFERING

Common stock offered by Epizyme 10,000,000 shares.

Common stock to be outstanding after this offering 89,230,173 shares.

Nasdaq Global Select Market symbol EPZM

Option to purchase additional shares The underwriters have an option to purchase up to an additional 1,500,000 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 \$106.6 million, or approximately \$122.6 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 and the Concurrent Offering, together with our existing cash, cash equivalents and marketable securities, to fund global development and commercialization costs of tazemetostat outside of Japan, including the costs of our ongoing and planned clinical trials of tazemetostat, the costs of regulatory activities related to tazemetostat, including associated milestone payments, the costs of conducting confirmatory programs to verify clinical benefit and support full approval of tazemetostat to the extent required by regulatory authorities, and the costs associated with the commercial launch of tazemetostat for epithelioid sarcoma and follicular lymphoma, if approved; to fund research and development costs to identify and develop other product candidates, including EZM8266 for sickle cell disease; 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-7 and in Part I, Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.

Concurrent Offering

Concurrently with this offering, we are conducting a public offering of 304,348 shares of our Series A preferred stock (and 3,043,480 shares of common stock issuable from time to time upon conversion of the Series A preferred stock). The Concurrent Offering is being conducted as a separate public offering by means of a separate prospectus supplement. This offering is not contingent upon the completion of the Concurrent Offering, and the Concurrent Offering is not contingent upon the completion of this offering.

The number of shares of our common stock to be outstanding after this offering is based on the 79,230,173 shares of our common stock outstanding as of February 28, 2019 and excludes:

6,991,600 shares of common stock issuable upon the exercise of stock options outstanding as of February 28, 2019, at a weighted average exercise price of \$12.67 per share;

S-5

Table of Contents

220,666 shares of common stock issuable upon the vesting of restricted stock units outstanding as of February 28, 2019;

6,323,587 shares of common stock that have been reserved for issuance in connection with future grants under our equity compensation plans as of February 28, 2019; and

3,043,480 shares of common stock issuable upon conversion of Series A preferred stock being offered by us in connection with the Concurrent Offering.

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.

Table of Contents

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 and in Part I, Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, 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 Our Common Stock and This Offering

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

Our stock price has been and may in the future be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. From January 1, 2016 until March 6, 2019, the sale price of our common stock as reported on the Nasdaq Global Select Market ranged from a high of \$28.48 to a low of \$5.14. 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 and in Part I, Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018.

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. Based on the public offering price of \$11.50 per share, you will experience immediate dilution of \$7.69 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. To the extent outstanding options are exercised at prices below the public offering price, you will incur further dilution.

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 Select Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for you to sell 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.

Table of Contents

We have broad discretion over the use of our cash and cash equivalents and marketable securities, including the net proceeds we receive in this offering and the Concurrent Offering, and may not use them effectively.

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

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 now that we are no longer an emerging growth company as of January 1, 2019, 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 Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and make some activities more time-consuming and costly.

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

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. Now that we are no longer an emerging growth company, we are also 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 have and will need to continue to dedicate internal resources, 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 or our auditors 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.

S-8

Table of Contents

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 \$106.6 million, or approximately \$122.6 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. In addition, we estimate that the net proceeds to us from our issuance and sale of shares of our Series A preferred stock in the Concurrent Offering will be approximately \$32.4 million, or approximately \$37.3 million if the underwriters exercise their option to purchase additional shares of Series A preferred stock in full, in each case after deducting underwriting discounts and commissions and estimated offering expenses payable by us. This offering is not contingent upon the completion of the Concurrent Offering, and the Concurrent Offering is not contingent upon the completion of this offering.

As of December 31, 2018, we had cash, cash equivalents and marketable securities of \$240.3 million. We intend to use the net proceeds from this offering and the Concurrent Offering, together with our existing cash, cash equivalents and marketable securities, as follows:

to fund global development costs of tazemetostat outside of Japan, including the costs of the following clinical trials and regulatory activities:

our global Phase 2 trial in patients with certain molecularly defined solid tumors, including our epithelioid sarcoma cohort in the trial, the preparation and submission of an NDA for accelerated approval for epithelioid sarcoma, and the initiation of a confirmatory clinical program, including the potential use of a natural history study, to verify clinical benefit and support the full approval of tazemetostat in patients with epithelioid sarcoma that could serve as a confirmatory trial as part of an accelerated approval strategy;

our global Phase 2 trial in patients with NHL, including our relapsed or refractory FL cohorts in the trial, continuing engagement with the FDA regarding the registration pathway in FL and preparation and submission of an NDA for accelerated approval for FL, and the initiation of a confirmatory clinical program to verify clinical benefit and support the full approval of tazemetostat for FL as part of an accelerated approval strategy and planned clinical trials to assess tazemetostat in earlier lines of treatment for FL; and

our planned clinical trials of tazemetostat in combination with other anti-cancer agents in multiple hematological malignancies and solid tumor indicators, including in castration-resistant prostate cancer and platinum-resistant solid tumors;

to fund the necessary pre-commercialization and launch related activities for tazemetostat and the execution of the initial commercial launch of tazemetostat for epithelioid sarcoma and relapsed and/or refractory follicular lymphoma, if approved;

to fund any milestone payments due under our amended and restated collaboration and license agreement with Eisai, including up to an aggregate of \$70 million in milestone payments associated with submission of NDAs in epithelioid sarcoma and FL and upon regulatory approval of tazemetostat for the treatment of epithelioid sarcoma and FL in the United States;

to fund research and development costs to develop other product candidates, including the costs of our planned initial clinical trial of EZM8266 for sickle cell disease; and

for working capital and other general corporate purposes.

This expected use of our net proceeds from this offering and the Concurrent 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 and the Concurrent Offering. We may find it necessary or advisable to use the net proceeds from this offering and the Concurrent Offering for other purposes, and we will have broad discretion in the application of net proceeds.

Table of Contents

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that the net proceeds from this offering and the Concurrent Offering, together with our existing cash, cash equivalents and marketable securities as of December 31, 2018, will enable us to fund our operating expenses and capital expenditure requirements at least into the first quarter of 2021. We believe that our available funds following this offering and the Concurrent Offering will be sufficient to enable us to complete our global Phase 2 trials in NHL and certain INI1-negative tumors, including the FL and epithelioid sarcoma cohorts in those trials; to submit NDAs to the FDA for tazemetostat for the treatment of epithelioid sarcoma and FL and to initiate confirmatory programs in both epithelioid sarcoma and FL; and to perform pre-commercialization activities and commercially launch tazemetostat for the treatment of epithelioid sarcoma and FL, if approved. However, it is possible that we will not achieve the progress that we expect with these funds because the actual costs and timing of clinical development, regulatory and commercial activities are difficult to predict and are subject to substantial risks and delays, and that we will use our capital resources sooner than we currently expect.

Pending our use of the net proceeds from this offering and the Concurrent 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.

S-10

Table of Contents**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, 2018 was \$233 million, or \$2.94 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 as of December 31, 2018.

After giving effect to our issuance and sale of 10,000,000 shares of common stock in this offering at the public offering price of \$11.50 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, 2018 would have been \$339.6 million, or \$3.81 per share. This represents an immediate increase of \$0.87 in as adjusted net tangible book value per share to existing stockholders and immediate dilution of \$7.69 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 or the sale of the Series A preferred stock in the Concurrent Offering and the conversion the Series A preferred stock into common stock:

Assumed public offering price per share	\$ 11.50
Net tangible book value per share as of December 31, 2018	\$ 2.94
Increase per share attributable to sale of shares of common stock in this offering	\$ 0.87
As adjusted net tangible book value per share after this offering	\$ 3.81
Dilution per share to new investors	\$ 7.69

If the underwriters exercise their option to purchase 1,500,000 additional shares in full at the public offering price of \$11.50 per share, the as adjusted net tangible book value will increase to \$3.92 per share, representing an immediate increase to existing stockholders of \$0.98 per share and an immediate dilution of \$7.58 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.

The above discussion and table do not take into account giving effect to the shares of Series A preferred stock offered by us in the Concurrent Offering. Giving effect to both this offering and the Concurrent Offering at the public offering price of \$115 per share (assuming no exercise of the underwriters' option to purchase additional shares and conversion

of all shares of Series A preferred stock offered in the Concurrent Offering), our as adjusted net tangible book value as of December 31, 2018 would have been approximately \$372.0 million, or \$4.03 per share of common stock, which represents an immediate increase in net tangible book value of \$1.09 per share of common stock to existing stockholders and immediate dilution in net tangible book value of \$7.47 per share of common stock to new investors participating in this offering.

S-11

Table of Contents

**MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS
OF
OUR COMMON STOCK**

The following is a 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 informational purposes 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 (other than a partnership or other entity or arrangement classified as a partnership for U.S. federal income tax purposes) 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. In addition, 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. 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 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, the alternative minimum tax, or the Medicare tax on net investment income. 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;

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;

persons who acquired our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; 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 entities or arrangements classified as partnerships 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.

S-12

Table of Contents

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.

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 (generally including provision of a valid IRS Form W-8ECI (or applicable successor form) certifying that the dividends are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States). 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 trade or business within the United States 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 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 five-year period ending

S-13

Table of Contents

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 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. Generally, a non-U.S. holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN or W-8BEN-E (or other applicable Form W-8) or otherwise meets the documentary evidence requirements for establishing that it is not a United States person or otherwise establishes an exemption. 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 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

Provisions of the Code commonly referred to as the Foreign Account Tax Compliance Act, or FATCA, generally 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 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.

S-14

Table of Contents

Withholding under FATCA generally will apply to payments of dividends on our common stock. While withholding under FATCA may apply to payments of gross proceeds from a sale or other disposition of our common stock, under recently proposed U.S. Treasury Regulations, withholding on payments of gross proceeds is not required. Although such regulations are not final, applicable withholding agents may rely on the proposed regulations until final regulations are issued.

If withholding under FATCA is required on any payment related to our common stock, investors not otherwise subject to withholding (or that otherwise would be entitled to a reduced rate of withholding) on such payment may be required to seek a refund or credit from the IRS. An intergovernmental agreement between the United States and an applicable foreign country may modify these rules. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock and the entities through which they hold our common stock.

The preceding discussion of material U.S. federal tax considerations is for informational purposes only. It is not legal or tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

Table of Contents**UNDERWRITING**

Subject to the terms and conditions set forth in the underwriting agreement, dated March 6, 2019, between us and Jefferies LLC, Citigroup Global Markets, Inc. and Cowen and Company, LLC, as the representatives of the underwriters named below and the joint book-running managers of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of our common stock shown opposite its name below:

UNDERWRITER	NUMBER OF SHARES
Jefferies LLC	3,450,000
Citigroup Global Markets Inc.	3,450,000
Cowen and Company, LLC	1,950,000
Wedbush Securities Inc.	800,000
H.C. Wainwright & Co., LLC	350,000
Total	10,000,000

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriting agreement provides that the underwriters will purchase all of the shares of common stock if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act of 1933, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that, following the completion of this offering, they currently intend to make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the common stock, that you will be able to sell any of the common stock held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the common stock subject to their acceptance of the common stock from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commission and Expenses

The underwriters have advised us that they propose to offer the common stock to the public at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers, which may include the underwriters or their affiliates, at that price less a concession not in excess of \$0.483 per share of common stock. After this offering, the initial public offering price, concession and reallocation to dealers may be reduced by the representative. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus supplement.

S-16

Table of Contents

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	PER SHARE		TOTAL	
	WITHOUT OPTION TO PURCHASE ADDITIONAL SHARES	WITH OPTION TO PURCHASE ADDITIONAL SHARES	WITHOUT OPTION TO PURCHASE ADDITIONAL SHARES	WITH OPTION TO PURCHASE ADDITIONAL SHARES
Public offering price	\$ 11.50	\$ 11.50	\$ 115,000,000	\$ 132,250,000
Underwriting discounts and commissions to be paid by us	\$ 0.805	\$ 0.805	\$ 8,050,000	\$ 9,257,500
Proceeds to us, before expenses	\$ 10.695	\$ 10.695	\$ 106,950,000	\$ 122,992,500

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$353,000. We have also agreed to reimburse the underwriters for certain of their expenses.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol EPZM .

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase, from time to time, in whole or in part, up to an aggregate of 1,500,000 shares from us at the public offering price set forth on the cover page of this prospectus supplement, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares proportionate to that underwriter's initial purchase commitment as indicated in the table above.

No Sales of Similar Securities

We, and our officers and directors, have agreed, subject to specified exceptions, not to directly or indirectly:

offer, sell, contract to sell, pledge or otherwise dispose of, or enter into any transaction that is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise) any shares of our capital stock or securities exchangeable or exercisable for or convertible into shares of our capital stock,

establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Securities Exchange Act of 1934, or the Exchange Act, and the rules and regulations of the SEC promulgated thereunder with respect to any shares of our capital stock or securities exchangeable or exercisable for or convertible into shares of our capital stock, or

publicly announce an intention to do any of the foregoing.

This restriction terminates after the close of trading of the common stock on and including the 60th day after the date of this prospectus supplement.

Jefferies LLC and Citigroup Global Markets, Inc. may, in their sole discretion and at any time or from time to time before the termination of the 60-day period release all or any portion of the securities subject to lock-up agreements. There are no existing agreements between the underwriters and any of our stockholders who will execute a lock-up agreement, providing consent to the sale of shares prior to the expiration of the lock-up period.

Stabilization

The underwriters have advised us that they, pursuant to Regulation M under the Exchange Act, and certain persons participating in this offering, may engage in short sale transactions, stabilizing transactions, syndicate covering

Table of Contents

transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either covered short sales or naked short sales.

Covered short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock 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 to purchase additional shares.

Naked short sales are sales in excess of the option to purchase additional shares of our common stock. 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 the shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with this offering. 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. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with this offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

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. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our common stock on The Nasdaq Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of shares of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us

or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriters and certain of their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The

S-18

Table of Contents

underwriters and certain of their respective affiliates have, from time to time, performed, and may in the future perform, various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and certain of their respective 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, and such investment and securities activities may involve securities and/or instruments issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the common stock offered hereby. Any such short positions could adversely affect future trading prices of the common stock offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Disclaimers About Non-U.S. Jurisdictions

Australia

This prospectus supplement is not a disclosure document for the purposes of Australia's Corporations Act 2001 (Cth) of Australia, or Corporations Act, has not been lodged with the Australian Securities & Investments Commission and is only directed to the categories of exempt persons set out below. Accordingly, if you receive this prospectus supplement in Australia:

A. You confirm and warrant that you are either:

a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;

a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to the company which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;

a person associated with the Company under Section 708(12) of the Corporations Act; or

a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act.

To the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act, any offer made to you under this prospectus supplement is void and incapable of acceptance.

- B. You warrant and agree that you will not offer any of the securities issued to you pursuant to this prospectus supplement for resale in Australia within 12 months of those securities being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Canada

- A. *Resale Restrictions.* The distribution of the shares in Canada is being made only in the provinces of Ontario, Quebec, Alberta and British Columbia on a private placement basis exempt from the requirement that we prepare and file a prospectus with the securities regulatory authorities in each province where trades of these securities are made. Any resale of the shares in Canada must be made under applicable securities laws which may vary depending on the relevant jurisdiction, and which may require resales to be made under available statutory exemptions or under a discretionary exemption granted by the applicable Canadian securities regulatory authority. Purchasers are advised to seek legal advice prior to any resale of the securities.

S-19

Table of Contents

- B. *Representations of Canadian Purchasers.* By purchasing shares in Canada and accepting delivery of a purchase confirmation, a purchaser is representing to and the dealer from whom the purchase confirmation is received that:

the purchaser is entitled under applicable provincial securities laws to purchase the shares of common stock without the benefit of a prospectus qualified under those securities laws as it is an accredited investor as defined under National Instrument 45-106 Prospectus Exemptions;

the purchaser is a permitted client as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations;

where required by law, the purchaser is purchasing as principal and not as agent; and

the purchaser has reviewed the text above under Resale Restrictions.

- C. *Conflicts of Interest.* Canadian purchasers are hereby notified that the underwriters are relying on the exemption set out in section 3A.3 or 3A.4, if applicable, of National Instrument 33-105 Underwriting Conflicts from having to provide certain conflict of interest disclosure in this document.
- D. *Statutory Rights of Action.* Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if the prospectus supplement (including any amendment thereto) such as this document contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser of these securities in Canada should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.
- E. *Enforcement of Legal Rights.* All of our directors and officers as well as the experts named herein may be located outside of Canada and, as a result, it may not be possible for Canadian purchasers to effect service of process within Canada upon us or those persons. All or a substantial portion of our assets and the assets of those persons may be located outside of Canada and, as a result, it may not be possible to satisfy a judgment against us or those persons in Canada or to enforce a judgment obtained in Canadian courts against us or those persons outside of Canada.
- F. *Taxation and Eligibility for Investment.* Canadian purchasers of shares of common stock should consult their own legal and tax advisors with respect to the tax consequences of an investment in the company in their particular circumstances and about the eligibility of the shares of common stock for investment by the purchaser under relevant Canadian legislation.

European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of shares of common stock 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 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 representative; 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 representative 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 to and with each of the representative and the Company 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 representative has been obtained to each such proposed offer or resale.

Table of Contents

For the purposes of this provision, the expression an offer of shares 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 (as amended by Directive 2010/73/EU), and includes any relevant implementing measure in the Relevant Member State.

Hong Kong

No securities have been offered or sold, and no securities may be offered or sold, in Hong Kong, by means of any document, other than to persons whose ordinary business is to buy or sell securities, whether as principal or agent; or to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong, or the SFO, and any rules made under that Ordinance; or in other circumstances which do not result in the document being a prospectus as defined in the Companies Ordinance (Cap. 32) of Hong Kong, or the CO, or which do not constitute an offer or invitation to the public for the purpose of the CO or the SFO. No document, invitation or advertisement relating to the securities has been issued or may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors as defined in the SFO and any rules made under that Ordinance.

This prospectus supplement has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus supplement may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this prospectus supplement and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

Israel

This document does not constitute a prospectus under the Israeli Securities Law, 5728-1968, or the Securities Law, and has not been filed with or approved by the Israel Securities Authority. In Israel, this prospectus is being distributed only to, and is directed only at, and any offer of the shares of common stock is directed only at, (i) a limited number of persons in accordance with the Israeli Securities Law and (ii) investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and qualified individuals, each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case, purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors are required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

Japan

This offering has not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948 of Japan, as amended), or FIEL, and the Initial Purchaser will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for

re-offering or resale, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the FIEL and any other applicable laws, regulations and ministerial guidelines of Japan.

Singapore

This prospectus supplement has not been and will not be lodged or registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares of common stock may not be circulated or distributed, nor may the shares of common stock be offered or sold, or be made the subject of an invitation for

S-21

Table of Contents

subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares of common stock are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- (a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor, securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the securities pursuant to an offer made under Section 275 of the SFA except:
 - i. to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
 - ii. where no consideration is or will be given for the transfer;
 - iii. where the transfer is by operation of law;
 - iv. as specified in Section 276(7) of the SFA; or
 - v. as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or the SIX, or on any other stock exchange or regulated trading facility in Switzerland. This prospectus supplement has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus supplement nor any other offering or marketing material relating to the securities or this offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus supplement nor any other offering or marketing material relating to this offering, the company or the securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus supplement will not be filed with, and the offer of securities will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, and the offer of securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or the CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of securities.

United Kingdom

This prospectus supplement is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the Order and other persons to whom it may lawfully be communicated (each such person being referred to as a relevant person).

This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Table of Contents

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.

S-23

Table of Contents

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements for the year ended December 31, 2018 included in our Annual Report on Form 10-K and the effectiveness of our internal control over financial reporting as of December 31, 2018. Such consolidated financial statements are incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our consolidated financial statements are incorporated by reference in reliance on their reports, given on their authority as experts in accounting and auditing.

S-24

Table of Contents

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.

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.

S-25

Table of Contents

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, 2018;

The information included in our definitive proxy statement on Schedule 14A for the 2018 Annual Meeting of Stockholders, filed on April 5, 2018, to the extent incorporated by reference into Part III of the Annual Report on Form 10-K for the fiscal year ended December 31, 2017;

Current Reports on Form 8-K filed on January 17, 2019 and March 1, 2019; 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

Table of Contents

PROSPECTUS

EPIZYME, INC.

Debt Securities

Common Stock

Preferred Stock

Units

Warrants

We may offer and sell securities from time to time in one or more offerings. 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 on page 5 of this prospectus, 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 April 5, 2018

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	2
<u>INCORPORATION BY REFERENCE</u>	2
<u>FORWARD-LOOKING STATEMENTS</u>	3
<u>EPIZYME, INC.</u>	4
<u>RISK FACTORS</u>	5
<u>CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES</u>	6
<u>USE OF PROCEEDS</u>	7
<u>DESCRIPTION OF DEBT SECURITIES</u>	8
<u>DESCRIPTION OF CAPITAL STOCK</u>	17
<u>DESCRIPTION OF UNITS</u>	23
<u>DESCRIPTION OF WARRANTS</u>	24
<u>FORMS OF SECURITIES</u>	25
<u>PLAN OF DISTRIBUTION</u>	27
<u>LEGAL MATTERS</u>	29
<u>EXPERTS</u>	29

Table of Contents

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.

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.

Table of Contents

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 (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, 2017, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2018 Annual Meeting of Stockholders; 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

Table of Contents

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, and Section 21E of the Securities Exchange Act. These statements may be identified by such forward-looking terminology as anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, should, continue, and similar terms or variations of such terms. Our forward-looking statements are based on a series of expectations, assumptions, estimates and projections about our company, are not guarantees of future results or performance and involve substantial risks and uncertainty. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. Our business and our forward-looking statements involve substantial known and unknown risks and uncertainties, including the risks and uncertainties inherent in our statements regarding:

our plans to develop and commercialize novel epigenetic therapies for patients with cancer and other serious diseases;

our ongoing and planned clinical trials, including the timing of initiation and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;

our ability to achieve anticipated milestones under our collaborations;

the timing of and our ability to apply for, obtain and maintain regulatory approvals for our product candidates;

the rate and degree of market acceptance and clinical utility of our products;

our commercialization, marketing and manufacturing capabilities and strategy;

our intellectual property position; and

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing. 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. An occurrence of or any material adverse change in one or more of such risk factors or risks and uncertainties could materially and adversely affect our business, prospects, financial condition and results of operations. All of our forward-looking statements are made as of the date hereof or thereof only. Actual results may differ materially from such forward-looking statements. We can give no assurance that such forward-looking statements will prove to be correct. 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.

Table of Contents

EPIZYME, INC.

We are a clinical-stage biopharmaceutical company that is committed to rewriting treatment for cancer and other serious diseases through discovering, developing, and commercializing novel epigenetic medicines. By focusing on the genetic drivers of disease, our science seeks to match targeted medicines with the patients who need them. We are broadly developing our lead product candidate, tazemetostat, an oral, first-in-class selective inhibitor of the EZH2 histone methyltransferase, or HMT, in a range of cancer types and settings, and developing the lead development candidate in our novel G9a program, EZM8266, for the treatment of sickle cell disease, or SCD.

We have taken a pipeline in a product approach to developing tazemetostat with a broad clinical development program through company-sponsored studies and collaborations that are evaluating tazemetostat as both a monotherapy and combination treatment in both hematological malignancies and solid tumors. Tazemetostat has shown meaningful clinical activity as a monotherapy in indications in both disease areas and has been well tolerated across clinical trials to date.

In our hematological malignancy program, we are conducting a global Phase 2 trial evaluating tazemetostat's treatment potential in patients with relapsed or refractory follicular lymphoma, or FL, or diffuse large B-cell lymphoma, or DLBCL, the two most prevalent forms of non-Hodgkin lymphoma, or NHL, both with and without EZH2 activating mutations. We are continuing to enroll FL and DLBCL patients with EZH2 mutations in our ongoing global Phase 2 monotherapy relapsed or refractory FL and DLBCL study. We also have multiple combination studies underway through collaborators with both targeted agents and chemotherapy in DLBCL, in both relapsed or refractory and first-line treatment settings.

In our solid tumor program, we are evaluating tazemetostat's treatment potential in adults and children with molecularly defined solid tumors, including INI1- and SMARCA4-negative tumors, which we collectively refer to as INI1-negative tumors. We are conducting a global Phase 2 trial of tazemetostat in adults with INI1-negative tumors, including epithelioid sarcoma, malignant rhabdoid tumors, or MRT, other INI1-negative tumors, and chordoma. We are also evaluating tazemetostat in the dose-expansion portion of a Phase 1 study in pediatric patients with INI1-negative tumors and in a Phase 2 study in adults with mesothelioma characterized by BAP1 loss-of-function. In addition, as part of a study conducted by our collaborator Genentech, Inc., or Genentech, tazemetostat is being evaluated in combination with atezolizumab, a PD-L1 inhibitor, in patients with non-small cell lung cancer, or NSCLC.

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

Table of Contents

RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks and uncertainties described under the section captioned Risk Factors contained in our most recent Annual Report on Form 10-K and other filings we make with the SEC from time to time, which are incorporated by reference herein, in their entirety together with other information in this prospectus, the information and documents incorporated by reference in this prospectus and in any prospectus supplement. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow 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.

Table of Contents**CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES**

The following table sets forth our consolidated 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.

(In thousands)	December 31, 2017	December 31, 2016	December 31, 2015	December 31, 2014	December 31, 2013
Net loss	\$ (134,309)	\$ (110,212)	\$ (132,376)	\$ (55,005)	\$ (3,483)
Consolidated ratios of earnings to fixed charges (1)	N/A	N/A	N/A	N/A	N/A
Coverage deficiency	\$ (134,309)	\$ (110,212)	\$ (132,376)	\$ (55,005)	\$ (3,483)

- (1) We did not record earnings for the years ended December 31, 2017, 2016, 2015, 2014 and 2013. 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.

Table of Contents

USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus to fund general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include the research and development of our product candidates, acquisition of companies or businesses, repayment and refinancing of debt, 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.

Table of Contents

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 requires, 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.

Neither 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 equally in right of payment 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 subordinated debt securities, the terms on which they are subordinated;

the initial 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;

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

Table of Contents

the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the method of determination of such 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 the debt securities will be subject to the defeasance provisions in the indenture;

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 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.

Table of Contents

Certain Terms of the Senior Debt Securities

Covenants. 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 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 with respect to a particular series of senior debt securities, 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, including the delivery to the senior trustee of an officer's certificate and an opinion of counsel, each stating that the consolidation, merger, conveyance, transfer or lease and if a supplemental indenture is required in connection with such transaction, such supplemental indenture, comply with the senior indenture and all conditions precedent provided for in the senior indenture relating to such transaction have been complied with.

The restrictions described in the bullets above do not apply (1) to our consolidation with or merging into one of our affiliates, if our board of directors determines in good faith that the purpose of the consolidation or merger is principally to change our state of incorporation or our form of organization to another form or (2) if we merge with or into single direct or indirect wholly owned subsidiary of ours.

The surviving business entity will succeed to, and be substituted for, us under the senior indenture and the senior debt securities and, except in the case of a lease, we shall be released from all obligations under the senior indenture and the senior debt securities.

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 with respect to senior debt securities of each series:

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;

Table of Contents

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.

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 automatically 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 a continuing 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 (other than any such default in payment resulting solely from an acceleration of the 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

Table of Contents

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. These limitations, however, do not apply to the right of any holder of a senior debt security of any affected series 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 (with certain limited exceptions);

we deliver to the senior trustee for cancellation all senior debt securities of such series theretofore authenticated under the senior indenture (with certain limited exceptions); 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 under arrangements satisfactory to the senior trustee) and we deposit in trust an amount of cash or a combination of cash and U.S. government or U.S. government agency obligations (or in the case of senior debt securities denominated in a foreign currency, foreign government securities or foreign government agency securities) 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; and if, in any such case, we also pay or cause to be paid all other sums payable under the senior indenture, as and when the same shall be due and payable and we deliver to the senior trustee an officer's certificate and an opinion of counsel, each stating that these conditions have been satisfied.

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 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 cash or a combination of cash and U.S. government or U.S. government agency obligations (or, in the case of senior debt securities denominated in a foreign currency, foreign government or foreign 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.

Table of Contents

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.

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 cash or a combination of cash and U.S. government or U.S. government agency obligations (or, in the case of senior debt securities denominated in a foreign currency, foreign government or foreign 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 of any series 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 (the *Trust Indenture Act*);

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, change or eliminate any of the provisions of the senior indenture in respect of one or more series of senior debt securities, provided that any such addition, change or elimination shall (a) neither (1) apply to any senior debt security of any series created prior to the execution of such supplemental indenture and entitled to the benefit of such provision nor (2) modify the rights of the holder of any such senior debt security with respect to such provision or (b) become effective only when there is no senior debt security described in clause (a)(1) outstanding;

Table of Contents

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.

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 each series affected by the amendment or modification (voting as separate series); 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 a continuing default in the payment of principal of or interest on the senior debt securities (other than any such default in payment resulting solely from an acceleration of the senior debt securities);

changes the provisions relating to the waiver of past defaults 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;

adversely affects the right to convert or exchange senior debt securities into common stock or other property in accordance with the terms of the senior debt securities; 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

Table of Contents

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.

The senior indenture and the provisions of the Trust Indenture Act 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, interest or additional amounts 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;

Table of Contents

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

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.

Table of Contents

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 March 31, 2018, 69,485,541 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.

Table of Contents

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.

Table of Contents

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.

Table of Contents

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;

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.

Table of Contents

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.

Table of Contents

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*.

Table of Contents

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.

Table of Contents

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.

Table of Contents

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 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.

Table of Contents

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.

Table of Contents

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.

Table of Contents

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 overallocate in connection with the offering, creating a short position for their own accounts. In addition, to cover overallocations 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 two 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 two 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 second 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 two scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

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.

Table of Contents

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. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

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, 2017, 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.

Table of Contents

10,000,000 Shares

Epizyme, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Jefferies

Citigroup
Lead Manager

Cowen

Wedbush PacGrow
Co-Manager

H.C. Wainwright & Co.

March 6, 2019