Epizyme, Inc.
Form 424B5
March 06, 2019
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Filed pursuant to Rule 424(b)(5)
Registration File No. 333-224159

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 6, 2019

Preliminary Prospectus Supplement

(To Prospectus Dated April 5, 2018)

Shares

Epizyme, Inc.

Series A Convertible Preferred Stock

$ Per Share

We are offering shares of our Series A convertible preferred stock, or the Series A preferred stock, and the common stock issuable from time to time upon conversion of our Series A preferred 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 5, 2019 was $12.29 per share. There is no established trading market for the Series A preferred stock, and we do not expect a market to develop. In addition, we do not intend to list the Series A preferred stock on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

Each share of Series A preferred stock is convertible into shares of our common stock at any time at the option of the holder, provided that the holder will be prohibited, subject to certain exceptions, from converting Series A preferred stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and other attribution parties, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. In the event of our liquidation, dissolution or winding up, holders of our Series A preferred stock will receive a payment equal to $0.001 per share of Series A preferred stock before any proceeds are

distributed to the holders of our common stock. In the event of a merger, consolidation, exchange offer or similar other transaction, the holders of the Series A preferred stock will receive the same consideration as the holders of our common stock, upon conversion of the Series A preferred stock. Shares of Series A preferred stock will generally have no voting rights, except as required by law and except that the consent of holders of a majority of the outstanding Series A preferred stock will be required to amend the terms of the Series A preferred stock.

Investing in our securities 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 Series A preferred stock, and pursuant to a separate prospectus supplement, we are also conducting a public offering (the Concurrent Offering) of shares of our common stock.

	PER SHARE	TOTAL
Public offering price	$	$
Underwriting discount[(1)]	$	$
Proceeds, before expenses, to Epizyme, Inc.	$	$

(1) We refer you to Underwriting beginning on page S-19 of this prospectus supplement for additional information regarding total underwriter compensation.

The underwriters expect to deliver the shares of Series A preferred stock to purchasers on or about , 2019.

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

Joint Book-Running Managers

Jefferies **Citigroup** **Cowen**

Lead Manager

Wedbush PacGrow

Co-Manager

H.C. Wainwright & Co.

Prospectus Supplement dated , 2019

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PROSPECTUS SUPPLEMENT

PROSPECTUS

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this Series A preferred 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 securities. 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 Series A preferred stock (and the underlying shares of 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 Series A preferred stock (and the underlying shares of 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 Series A preferred stock (and the underlying shares of common stock) and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

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

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

The forward-looking statements in this prospectus supplement, 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.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference herein and therein. This summary does not contain all of the information you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our securities discussed under Risk Factors beginning on page S-7 of this prospectus supplement and in Part I, Item IA 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

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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

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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 IA 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.

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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 Common Stock

Concurrently with this offering of Series A preferred stock, we are conducting a public offering of shares of our common 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.

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THE OFFERING

Series A preferred stock offered by Epizyme	shares. This prospectus supplement also relates to the offering of shares of common stock issuable upon conversion of the Series A preferred stock.
Option to purchase additional shares	The underwriters have an option to purchase up to an additional shares of our Series A preferred stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Conversion	Each share of our Series A preferred stock is convertible into shares of our common stock at any time at the option of the holder, provided that the holder will be prohibited, subject to certain exceptions, from converting Series A preferred stock if, as a result of such conversion, the holder, together with its affiliates and other attribution parties, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding, which percentage may be changed at the holders election to a higher or lower percentage upon 61 days notice to us.
Liquidation preference	In the event of our liquidation, dissolution, or winding up, holders of our Series A preferred stock will receive a payment equal to $0.001 per share of Series A preferred stock before any proceeds are distributed to the holders of our common stock.
Voting rights	Shares of Series A preferred stock will generally have no voting rights except as required by law and except that the consent of the holders of a majority of our outstanding shares of Series A preferred stock will be required to amend the terms of the Series A preferred stock or take certain other actions with respect to the Series A preferred stock.
Dividends	Shares of Series A preferred stock will be entitled to receive dividends equal to (on an as-if-converted-to-common stock basis), and in the same form and manner as, dividends actually paid on shares of our common stock.
Use of proceeds	We estimate that the net proceeds to us from this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us will be approximately

$ million, or approximately $ 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

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	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 IA 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 our securities.
Concurrent Offering	Concurrently with this offering, we are conducting a public offering of shares of our common 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.
Listing	There is no established public trading market for the Series A preferred stock, and we do not expect a market to develop. In addition, we do not intend to apply for listing of the Series A preferred stock on The Nasdaq Global Select Market or on any national securities or other nationally recognized trading system. Our common stock is listed on The Nasdaq Global Select Market under the symbol EPZM.

There are no shares of Series A preferred stock issued or outstanding prior to this offering. The number of shares of our common stock outstanding as of February 28, 2019 was 79,230,173 shares 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;
- 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;
- shares of our common stock being offered in the Concurrent Offering; and

shares of our common stock issuable upon the conversion of the Series A preferred stock being offered by us in connection with this 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 in this offering or in the Concurrent Offering.

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RISK FACTORS

Investing in our securities involves a high degree of risk. Before you decide to invest in our securities, you should carefully consider the risks and uncertainties described below and in Part I, Item IA 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 (including the common stock issuable upon conversion of the Series A preferred stock issued in this offering) could decline and you might lose all or part of your investment.

Risks Related to Our Securities 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 February 28, 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 IA of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018.

If you purchase shares of Series A preferred stock in this offering, assuming the conversion into shares of our common stock, you will suffer immediate dilution of your investment.

The public offering price per share attributable to each share of common stock issuable upon conversion of our Series A preferred stock being offered 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 Series A preferred stock in this offering you will suffer immediate and substantial dilution in the net tangible book value of the common stock issuable upon the conversion of Series A preferred stock you purchase in this offering. Based on the public offering price of $ per share and our net tangible book value as of December 31, 2018, assuming the conversion of shares of our Series A preferred stock to be issued in this offering into shares of common stock, but excluding the effect of shares of common stock to be issued in the Concurrent Offering, you will experience immediate dilution of $ 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.

There is no public market for the Series A preferred stock in this offering.

There is no established public trading market for the Series A preferred stock being offered in this offering, and we do not expect a market to develop. In addition, we do not intend to apply for listing of the Series A preferred stock

on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system. Without an active market, the liquidity of the Series A preferred stock will be limited.

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 any shares of common stock issuable upon conversion of shares of Series A preferred stock purchased in this offering. 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.

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.

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

The trading market for our common stock may be impacted, in part, by the research and reports that securities or industry analysts publish about us or our business. There can be no assurance that analysts will cover us, continue to cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price may decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

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USE OF PROCEEDS

We estimate that the net proceeds to us from our issuance and sale of shares of our Series A preferred stock in this offering will be approximately $ million, or approximately $ 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 common stock in the Concurrent Offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares of common 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. 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.

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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.

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DILUTION

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 shares of our Series A preferred stock in this offering at the public offering price of $ per share, assuming the conversion of all shares of our Series A preferred stock sold in this offering into shares of our common stock, and after deducting estimated 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 $ million, or $ per share. This represents an immediate increase of $ in as adjusted net tangible book value per share to existing stockholders and immediate dilution of $ in as adjusted net tangible book value per share of common stock to new investors purchasing common stock into which the shares of Series A preferred stock are convertible. 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 in this offering without giving effect to any exercise by the underwriters of their option to purchase additional shares:

Assumed public offering price per share of common stock into which the shares of Series A preferred stock being offered in this offering are convertible		$
Net tangible book value per share of common stock as of December 31, 2018	$ 2.94	
Increase in net tangible book value per share of common stock attributable to investors purchasing Series A preferred stock in this offering	$	
As adjusted net tangible book value per share of common stock after this offering		$
Dilution per share of common stock to new investors purchasing Series A preferred stock in this offering		$

A $1.00 increase (decrease) in the public offering price of $ per share would increase (decrease) dilution per share to new investors by approximately $ after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

If the underwriters exercise their option to purchase additional shares in full at the public offering price of

$ per share, the as adjusted net tangible book value will increase to $ per share, representing an immediate

increase to existing stockholders of $ per share and an immediate dilution of $ 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 common stock offered by us in the Concurrent Offering. Giving effect to both this offering and the Concurrent Offering at the public offering price of $ per share (assuming no exercise of the underwriters option to purchase additional shares in this offering or in the Concurrent Offering), our as adjusted net tangible book value as of December 31 2018, would have been approximately $, or $ per share of common stock (assuming conversion of all shares of Series A preferred stock offered in this offering), which represents an immediate decrease in net tangible book value of $ per share of common stock to existing stockholders and immediate dilution in net tangible book value of $ per share of common stock into which the shares of Series A preferred stock are convertible to investors participating in this offering.

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DESCRIPTION OF SECURITIES WE ARE OFFERING

We are offering shares of Series A preferred stock. The common stock issuable upon conversion of the Series A preferred stock offered by this prospectus supplement and the accompanying prospectus is described in the accompanying prospectus under the heading Description of Our Capital Stock. The Series A preferred stock offered by this prospectus supplement and the accompanying prospectus are described in the immediately following section of this prospectus supplement.

Series A Preferred Stock

The following summary of certain terms and provisions of our Series A preferred stock offered in this offering is subject to, and qualified in its entirety by reference to, the terms and provisions set forth in our certificate of designation of preferences, rights and limitations of Series A preferred stock that we expect to file as an exhibit to a Current Report on Form 8-K.

General. Our certificate of incorporation authorizes our board of directors to issue up to 5,000,000 shares of our preferred stock, par value $0.0001 per share.

Subject to the limitations prescribed by our certificate of incorporation, our board of directors is authorized to establish the number of shares constituting each series of preferred stock and to fix the designations, powers, preferences and rights of the shares of each of those series and the qualifications, limitations and restrictions of each of those series, all without any further vote or action by our stockholders. Our board of directors has designated of the 5,000,000 authorized shares of preferred stock as Series A preferred stock. When issued, the shares of Series A preferred stock will be validly issued, fully paid and non-assessable.

Rank. The Series A preferred stock will rank:

- senior to all of our common stock;
- senior to any class or series of our capital stock hereafter created specifically ranking by its terms junior to the Series A preferred stock;
- on parity with any class or series of capital stock hereafter created specifically ranking by its terms on parity with the Series A preferred stock; and
- junior to any class or series of capital stock hereafter created specifically ranking by its terms senior to the Series A preferred stock;

in each case, as to distributions of assets upon our liquidation, dissolution or winding up, whether voluntarily or involuntarily.

Conversion. Each share of the Series A preferred stock is convertible into shares of our common stock (subject to adjustment as provided in the related certificate of designation of preferences, rights and limitations) at any time at the option of the holder, provided that the holder will be prohibited, subject to certain exceptions, from

converting Series A preferred stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and other attribution parties, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding, which percentage may be changed at the holders election to a higher or lower percentage upon 61 days notice to us.

Liquidation Preference. In the event of our liquidation, dissolution or winding up, holders of the Series A preferred stock will receive a payment equal to $0.001 per share of Series A preferred stock before any proceeds are distributed to the holders of our common stock.

Fundamental Transaction. Upon consummation of a Fundamental Transaction (as defined below), each outstanding share of Series A preferred stock shall be cancelled and the holder thereof shall have the right to receive, in lieu of the right to receive the shares of our common stock underlying the Series A preferred stock, for each share of common stock that it would have otherwise been entitled to receive upon such conversion immediately prior to the occurrence of such Fundamental Transaction, the same kind and amount of securities, cash or property as it would

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have been entitled to receive upon the occurrence of such Fundamental Transaction if it had been, immediately prior to such Fundamental Transaction, the holder of one share of our common stock. If holders of our common stock are given a choice as to the securities, cash or property to be received in a Fundamental Transaction, then the holder of the Series A preferred stock shall be given the same choice as to the consideration it receives upon any exercise of the Series A preferred stock following such Fundamental Transaction.

A Fundamental Transaction means:

- we effect any merger or consolidation with or into another person (other than such a transaction in which we are the surviving or continuing entity and our common stock is not exchanged for or converted into other securities, cash or property);
- we effect any sale lease, license, assignment, transfer, conveyance or other disposition of all or substantially all of our assets in one transaction or a series of related transactions;
- any tender offer or exchange offer (whether by us or another person) is completed pursuant to which more than 50% of the common stock not held by us or such person is exchanged for or converted into other securities, cash or property;
- we effect any reclassification, reorganization or recapitalization of our common stock or any compulsory share exchange pursuant (other than specified dividends, subdivisions or combinations) to which our common stock is effectively converted into or exchanged for other securities, cash or property; or
- we consummate a stock or share purchase agreement or other business combination with another person whereby such person acquires more than 50% of our outstanding common stock.

Voting Rights. Shares of Series A preferred stock will generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series A preferred stock will be required to amend the terms of the Series A preferred stock or take certain other actions with respect to the Series A preferred stock.

Dividends. Share of Series A preferred stock will be entitled to receive dividends equal to (on an as-if-converted-to-common stock basis), and in the same form and manner as, dividends actually paid on shares of common stock.

Redemption. We are not obligated to redeem or repurchase any shares of Series A preferred stock. Shares of Series A preferred stock are not otherwise entitled to any redemption rights or mandatory sinking fund or analogous fund provisions.

Exchange Listing. We do not intend to list the Series A preferred stock on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system. We expect the common stock issuable upon conversion of the Series A preferred stock to be listed on The Nasdaq Global Select Market.

Transfer Agent and Registrar

The transfer agent and registrar for shares of our Series A preferred stock (and the underlying shares of common stock) is Computershare Trust Company, Inc.

Listing on The Nasdaq Global Select Market

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol EPZM. There is no established public trading market for the Series A preferred stock, and we do not expect a market to develop. We do not intend to list the Series A preferred stock on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

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MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF OUR SERIES A PREFERRED 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, disposition and conversion of shares of our Series A preferred stock and any common stock received in respect of Series A preferred stock. This discussion is for informational purposes only and is not tax advice. Accordingly, all prospective non-U.S. holders of our Series A preferred stock or 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, disposition or conversion of our Series A preferred stock or 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 Series A preferred stock or 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 Series A preferred stock or 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 Series A preferred stock or common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;

persons who acquired our Series A preferred stock or 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 Series A preferred stock or 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 Series A

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preferred stock or common stock should consult his, her or its own tax advisor regarding the tax consequences of acquiring, holding and disposing of our Series A preferred stock or common stock through a partnership or other pass-through entity, as applicable.

Distributions

Distributions on our Series A preferred stock or 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 Series A preferred stock or common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in Disposition of Our 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 Series A preferred stock or 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.

Disposition of Our 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 Series A preferred stock or 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 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

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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 on the date of the taxable disposition or the period that the non-U.S. holder held our Series A preferred stock or 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.

Conversion of Series A Preferred Stock into Common Stock

A non-U.S. holder generally will not recognize gain or loss upon the conversion of our Series A preferred stock into shares of our common stock, except with respect to any cash received in lieu of a fractional share of our common stock. A non-U.S. holder s receipt of cash in lieu of a fractional share of our common stock will result in capital gain or loss (measured by the difference between the cash received in lieu of the fractional share of our common stock and the non-U.S. holder s tax basis in the fractional share of our common stock). Any such capital gain will be subject to the tax treatment described above in Disposition of Our Stock.

Adjustment to Conversion Rate of Series A Preferred Stock

The conversion rate of our outstanding Series A preferred stock is subject to adjustment under specified circumstances. Adjustments (or failure to make adjustments) that have the effect of increasing a non-U.S. holder s proportionate interest in our assets or earnings and profits may, in some circumstances, result in a constructive distribution to the non-U.S. holder. Adjustments to the conversion rate made pursuant to a bona fide reasonable adjustment formula which has the effect of preventing the dilution of the interest of the holders of our Series A preferred stock generally will not be deemed to result in a constructive distribution. If an adjustment is made that does not qualify as being made pursuant to a bona fide reasonable adjustment formula, a non-U.S. holder of our Series A preferred stock may be deemed to have received a constructive distribution from us, even though such U.S. holder has not received any cash or property as a result of such adjustment. The tax consequences of the receipt of a distribution from us are described above under Distributions. Any resulting withholding tax attributable to deemed dividends would be collected from other amounts payable or distributable to the non-U.S. holder.

U.S. Federal Estate Tax

Shares of our Series A preferred stock or 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 Series A preferred stock or 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 Series A preferred stock or 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 a not a United States

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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, 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 Series A preferred stock or 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 Series A preferred stock or 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.

Withholding under FATCA generally will apply to payments of dividends on our Series A preferred stock or common stock. While withholding under FATCA may apply to payments of gross proceeds from a sale or other disposition of our Series A preferred stock or 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 Series A preferred stock or 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 Series A preferred stock or common stock and the entities through which they hold our Series A preferred stock or 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 Series A preferred stock or common stock, including the consequences of any proposed changes in applicable laws.

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UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated , 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 Series A preferred stock shown opposite its name below:

UNDERWRITER	NUMBER OF SHARES
Jefferies LLC	
Citigroup Global Markets Inc.	
Cowen and Company, LLC	
Wedbush Securities Inc.	
H.C. Wainwright & Co., LLC	
Total	

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 Series A preferred 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 are offering the Series A preferred stock subject to their acceptance of the Series A preferred 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 Series A preferred stock to the public at the public offering price set forth on the cover page of this prospectus supplement. After this offering, the public offering price may be reduced by the representatives. 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.

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	$	$	$	$
Underwriting discounts and commissions to be paid by us	$	$	$	$
Proceeds to us, before expenses	$	$	$	$

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

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Listing

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol EPZM. There is no established public trading market for the Series A preferred stock, and we do not expect a market to develop. We do not intend to list the Series A preferred stock on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

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 Series A preferred 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 Series A preferred 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.

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 Series A preferred 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 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.

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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 Series A preferred stock offered hereby. Any such short positions could adversely affect future trading prices of the Series A preferred 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.

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 Series A preferred 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;

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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 Series A preferred 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 Series A preferred 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 Series A preferred 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.

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.

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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 Series A preferred 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 Series A preferred stock may not be circulated or distributed, nor may the shares of Series A preferred stock be offered or sold, or be made the subject of an invitation for 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.

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Where the shares of Series A preferred 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.

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LEGAL MATTERS

The validity of the securities 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.

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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.

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WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at http://www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at http://www.epizyme.com. Our website is not a part of this prospectus 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.

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INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

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

- Annual Report on Form 10-K for the fiscal year ended December 31, 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

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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

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