

PROSPECTUS



5,653,000 SHARES OF COMMON STOCK

This prospectus relates to the resale, from time to time, of up to 5,653,000 shares of common stock issuable upon exercise of a warrant previously issued by Epizyme, Inc. to the selling stockholder, Hutchison China MediTech Investment Limited, which we refer to as Hutchmed or the selling stockholder.

We will not receive any proceeds from the sale of the shares.

The selling stockholder identified in this prospectus, or its pledgees, assignees, donees, transferees or other successors-in-interest, may offer the shares from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "EPZM". On September 29, 2021, the closing sale price of the common stock on The Nasdaq Global Select Market was \$5.13 per share. You are urged to obtain current market quotations for the common stock.

Investing in our common stock involves a high degree of risk. See ["Risk Factors"](#) beginning on page 4.

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.

The date of this prospectus is September 29, 2021.

TABLE OF CONTENTS

	<u>Page</u>
Special Note Regarding Forward-Looking Information	1
Prospectus Summary	2
The Offering	3
Risk Factors	4
Use Of Proceeds	5
Selling Stockholder	6
Description Of Capital Stock	7
Plan Of Distribution	10
Legal Matters	12
Experts	12
Where You Can Find More Information	13
Incorporation Of Certain Documents By Reference	14

We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. The selling stockholder is offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING INFORMATION

This prospectus includes and incorporates forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, included or incorporated in this prospectus regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The words “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will 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 or incorporated in this prospectus, particularly under the heading “Risk Factors”, 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. Any such forward-looking statements represent management’s views as of the date of the document in which such forward-looking statement is contained. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

PROSPECTUS SUMMARY

This summary highlights important features of this offering and the information included or incorporated by reference in this prospectus. This summary does not contain all of the information that you should consider before investing in our common stock. You should read the entire prospectus carefully, especially the risks of investing in our common stock discussed under “Risk Factors.”

Epizyme, Inc.

We are a commercial-stage biopharmaceutical company that is committed to rewriting treatment for people with cancer through the discovery, development, and commercialization of novel epigenetic medicines. We aspire to change the standard of care for patients and physicians by developing targeted medicines with fundamentally new mechanisms of action directed at specific causes of hematological malignancies and solid tumors.

We have one United States Food and Drug Administration, or FDA, approved product, TAZVERIK® (tazemetostat), for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma who are not eligible for complete resection; adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies; and adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Corporate Information

We were incorporated under the laws of the State of Delaware on November 1, 2007 under the name Epizyme, Inc. Our principal executive offices are located at 400 Technology Square, 4th Floor, 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. We have included our website address in this prospectus solely as an inactive textual reference.

Unless the context otherwise requires references in this prospectus to “Epizyme,” “we,” “us,” and “our” refer to Epizyme, Inc. and its consolidated subsidiary.

Epizyme® and TAZVERIK® are registered trademarks of Epizyme, Inc. in the United States and other countries. Epizyme, Inc. has also submitted trademark applications for Epizyme™ and TAZVERIK™ in other countries.

THE OFFERING

Common Stock offered by selling stockholders	5,653,000 shares
Use of proceeds	Epizyme will not receive any proceeds from the sale of shares in this offering
Nasdaq Global Select Market symbol	“EPZM”

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should consider carefully the risks and uncertainties described under the section captioned “Risk Factors” contained in our most recent [Annual Report](#) on Form 10-K and other filings we make with the Securities and Exchange Commission, or SEC, from time to time, which are incorporated by reference herein in their entirety, together with other information in this prospectus, the information and documents incorporated by reference in this prospectus, and in any prospectus supplement. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could suffer materially.

USE OF PROCEEDS

We will not receive any proceeds from the sale of shares by the selling stockholder.

The selling stockholder will pay any underwriting discounts and commissions and expenses incurred by the selling stockholder for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholder in disposing of the shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including, without limitation, all registration and filing fees, the Nasdaq Global Select Market listing fees and fees and expenses of our counsel and our accountants.

SELLING STOCKHOLDER

This prospectus relates to the possible resale by Hutchmed of shares of our common stock that are issuable upon exercise of a warrant we issued to Hutchmed in a private placement. The following table sets forth, to our knowledge, certain information about the selling stockholder as of August 31, 2021.

Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to shares. Shares of common stock issuable under warrants that are exercisable within 60 days after August 31, 2021 are deemed outstanding for computing the percentage ownership of the person holding the warrants but are not deemed outstanding for computing the percentage ownership of any other person. Unless otherwise indicated below, to our knowledge, the selling stockholder has sole voting and investment power with respect to their shares of common stock, except to the extent authority is shared by spouses under applicable law. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below.

Name of Selling Stockholder	Shares of Common Stock Beneficially Owned Prior to Offering		Number of Shares of Common Stock Being Offered	Shares of Common Stock to be Beneficially Owned After Offering (1)	
	Number	Percentage		Number	Percentage
Hutchison China MediTech Investment Limited (2)	5,653,000	5.5%	5,653,000	0	0.0%

- (1) We do not know when or in what amounts the selling stockholder may offer shares for sale. The selling stockholder might not sell any or all of the shares offered by this prospectus. Because the selling stockholder may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholder after completion of the offering. However, for purposes of this table, we have assumed that, after completion of the offering, none of the shares covered by this prospectus will be held by the selling stockholder.
- (2) Consists of 5,653,000 shares of common stock issuable upon the exercise of a warrant to purchase common stock exercisable within 60 days after August 31, 2021. The address of Hutchison China MediTech Investment Limited is Level 18, The Metropolis Tower, 10 Metropolis Drive, Kowloon, Hong Kong.

Description of Transactions with the Selling Stockholder

On August 7, 2021, we entered into a license agreement with the selling stockholder for the development, manufacture and commercialization of tazemetostat, either as a monotherapy or as a part of combinations with other therapies, including proprietary compounds of the selling stockholder, agreed by the parties under the license agreement for the treatment of epithelioid sarcoma, follicular lymphoma, diffuse large B-cell lymphoma in humans, and any additional indications agreed by the parties in accordance with the terms of the license agreement in mainland China, Taiwan, Hong Kong and Macau. Under the license agreement, we issued to the selling stockholder a warrant to purchase up to 5,653,000 shares of our common stock at an exercise price of \$11.50 per share, exercisable at any time on or before August 7, 2025. This prospectus relates to the possible resale by the selling stockholder of shares of our common stock that are issuable upon exercise of the warrant.

DESCRIPTION OF CAPITAL STOCK

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

Our authorized capital stock consists of 225,000,000 shares of common stock, par value \$0.0001 per share, and 5,000,000 shares of preferred stock, par value \$0.0001 per share, 4,662,200 of which preferred stock is undesignated.

As of August 31, 2021, 102,249,517 shares of common stock were outstanding and 337,800 shares of preferred stock were outstanding.

Common Stock

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

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

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

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

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

Listing on the Nasdaq Global Select Market. Our common stock is listed on the Nasdaq Global Select Market under the symbol “EPZM.”

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

Delaware law contains, and our restated certificate of incorporation and our bylaws contain, provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These

[Table of Contents](#)

provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

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

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

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

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

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

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

The prohibition against these transactions does not apply if:

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

[Table of Contents](#)

Amendment of Restated Certificate of Incorporation and Bylaws. The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's restated certificate of incorporation or bylaws, unless a corporation's restated certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described above under "Removal of Directors" and "Stockholder Action by Written Consent; Special Meetings."

PLAN OF DISTRIBUTION

The shares covered by this prospectus may be offered and sold from time to time by the selling stockholder. The term “selling stockholder” includes donees, pledgees, assignees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer. The selling stockholder will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges in any market or trading facility on which the shares are traded, or in the over-the-counter market or otherwise, at fixed prices, at prices and under terms then prevailing or at prices related to the then current market price or in negotiated transactions. The selling stockholder may sell its shares by one or more of, or a combination of, the following methods:

- purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- an over-the-counter distribution in accordance with the rules of the Nasdaq Global Select Market;
- in privately negotiated transactions; and
- in options transactions.

In addition, any shares that qualify for sale pursuant to Rule 144 may be sold under Rule 144 rather than pursuant to this prospectus.

To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with distributions of the shares or otherwise, the selling stockholder may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of the common stock in the course of hedging the positions they assume with the selling stockholder. The selling stockholder may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholder may also enter into option or other transactions with broker-dealers or other financial institutions which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The selling stockholder may also pledge or grant a security interest in shares to a broker-dealer, other financial institution or other person, and, upon a default such pledgee or secured parties may effect sales of the pledged shares pursuant to this prospectus (as supplemented or amended to reflect such transaction).

In effecting sales, broker-dealers or agents engaged by the selling stockholder may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling stockholder in amounts to be negotiated immediately prior to the sale.

In offering the shares covered by this prospectus, the selling stockholder and any broker-dealers who execute sales for the selling stockholder may be deemed to be “underwriters” within the meaning of the Securities Act in connection with such sales. The compensation of any broker-dealer may be deemed to be underwriting discounts and commissions.

In order to comply with the securities laws of certain states, if applicable, the shares must be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in certain states the shares may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

Table of Contents

We have advised the selling stockholder that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholder and its affiliates. In addition, we will make copies of this prospectus available to the selling stockholder for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholder may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

At the time a particular offer of shares is made, if required, a prospectus supplement will be distributed that will set forth the number of shares being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallocated or paid to any dealer, and the proposed selling price to the public.

We have agreed to indemnify the selling stockholder against certain liabilities, including certain liabilities under the Securities Act.

We have agreed with the selling stockholder to keep the Registration Statement of which this prospectus constitutes a part effective until the earlier of (i) such time as all of the shares covered by this prospectus have been disposed of pursuant to and in accordance with the Registration Statement, (ii) such time as all of the shares covered by this prospectus have been sold pursuant to Rule 144 under the Securities Act under circumstances in which any legend borne by such shares relating to restrictions on transferability thereof, under the Securities Act or otherwise, is removed by the Company, (iii) such time as all of the shares covered by this prospectus are eligible to be sold pursuant to Rule 144 under the Securities Act without condition or restriction, including without any limitation as to volume of sales, and without the selling stockholder complying with any method of sale requirements or notice requirements under Rule 144 under the Securities Act, or (iv) such time as all of the shares covered by this prospectus shall cease to be outstanding following their issuance.

LEGAL MATTERS

The validity of the shares offered by this prospectus has been passed upon by Wilmer Cutler Pickering Hale and Dorr LLP.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020 and the effectiveness of our internal control over financial reporting as of December 31, 2020, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

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

This prospectus is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus regarding us and our common stock, 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.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC requires us to “incorporate” into this prospectus information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus. Information contained in this prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus automatically updates and supersedes previously filed information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and prior to the sale of all the shares covered by this prospectus.

- (1) Our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2020, including the information specifically incorporated by reference into our Annual Report on Form 10-K from our [definitive proxy statement](#) for our 2021 Annual Meeting of Stockholders;
- (2) Our Quarterly Report on [Form 10-Q](#) for the fiscal quarter ended March 31, 2021;
- (3) Our Quarterly Report on [Form 10-Q](#) for the fiscal quarter ended June 30, 2021;
- (4) Our Current Reports on Form 8-K dated [June 16, 2021](#), [June 28, 2021](#), [August 9, 2021](#) and [August 16, 2021](#); and
- (5) The description of our common stock contained in our Registration Statement on [Form 8-A](#) filed on May 24, 2013, as the description therein has been updated and superseded by the description of our capital stock contained in [Exhibit 4.4](#) to our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, as filed with the SEC on February 27, 2020, and including any amendments and reports filed for the purpose of updating such description.

A statement contained in a document incorporated by reference into this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or in any other subsequently filed document which is also incorporated in this prospectus modifies or replaces such statement. Any statements so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

You may request a copy of these documents, which will be provided to you at no cost, by writing or telephoning us using the following contact information:

Epizyme, Inc.
400 Technology Square, 4th Floor
Cambridge, Massachusetts 02139
Attn: Investor Relations
617-229-5872



**5,653,000 Shares of
Common Stock**

PROSPECTUS

September 29, 2021
