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As filed with the Securities and Exchange Commission on September 21, 2021

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

EPIZYME, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware **(State or Other Jurisdiction of Incorporation or Organization)**	**26-1349956** **(I.R.S. Employer Identification Number)**

400 Technology Square, 4th Floor
Cambridge, Massachusetts 02139
617-229-5872
(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

Grant Bogle
President and Chief Executive Officer
Epizyme, Inc.
400 Technology Square, 4th Floor
Cambridge, Massachusetts 02139
617-229-5872
(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent for Service)

Copies to:

John Weidenbruch **Epizyme, Inc** **400 Technology Square, 4th Floor** **Cambridge, Massachusetts 02139** **Telephone: (617) 401-0746** **Facsimile: (617) 349-0707**	**Stuart M. Falber, Esq.** **Molly W. Fox, Esq.** **Wilmer Cutler Pickering Hale and Dorr LLP** **60 State Street** **Boston, MA 02109** **Telephone: (617) 526-6000** **Facsimile: (617) 526-5000**

Approximate date of commencement of proposed sale to the public: From time to time after the effective date hereof.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. ☐

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. ☒

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. ☐

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. ☐

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act. ☐

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	**Amount to be Registered (1)**	**Proposed Maximum Offering Price Per Share (2)**	**Proposed Maximum Aggregate Offering Price (2)**	**Amount of Registration Fee**
Common Stock, $0.0001 par value per share	5,653,000	$5.28	$29,847,840	$3,256.40

(1) This Registration Statement relates to 5,653,000 shares of the Registrant's common stock issuable upon the exercise of a warrant to purchase common stock, which shares of common stock will be offered for resale by the selling stockholder. Pursuant to Rule 416 under the Securities Act, this Registration Statement also relates to an indeterminate number of additional shares of the Registrant's common stock to be issued as a result of stock splits, stock dividends or similar transactions.

(2) Estimated solely for purposes of calculating the registration fee pursuant to Rule 457(c) under the Securities Act, based on the average of the high and low price per share of the Registrant's common stock as reported on the Nasdaq Global Select Market on September 16, 2021.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information in this prospectus is not complete and may be changed. The selling stockholder named in this prospectus may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and the selling stockholder named in this prospectus is not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated September 21, 2021

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 20, 2021, the closing sale price of the common stock on The Nasdaq Global Select Market was $5.49 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 , 2021.

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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.

	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)	
Name of Selling Stockholder	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

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

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

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

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

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

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

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

The prohibition against these transactions does not apply if:

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

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

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.

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 reallowed 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

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

The following table sets forth the various expenses to be incurred in connection with the sale and distribution of the securities being registered hereby, all of which will be borne by Epizyme, Inc. (except 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). All amounts shown are estimates except the SEC registration fee.

SEC registration fee	$ 3,256.40
Legal fees and expenses	$ 15,000
Accounting fees and expenses	$ 8,000
Miscellaneous expenses	$ 1,743.60
Total expenses	$ 28,000

Item 15. Indemnification of Directors and Officers.

Section 102 of the Delaware General Corporation Law permits a corporation to eliminate the personal liability of its directors or its stockholders for monetary damages for a breach of fiduciary duty as a director, except where the director breached his or her duty of loyalty, failed to act in good faith, engaged in intentional misconduct or knowingly violated a law, authorized the payment of a dividend or approved a stock repurchase in violation of Delaware corporate law or obtained an improper personal benefit. Our restated certificate of incorporation provides that no director shall be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duty as a director, notwithstanding any provision of law imposing such liability, except to the extent that the Delaware General Corporation Law prohibits the elimination or limitation of liability of directors for breaches of fiduciary duty.

Section 145 of the Delaware General Corporation Law provides that a corporation has the power to indemnify a director, officer, employee or agent of the corporation and certain other persons serving at the request of the corporation in related capacities against expenses (including attorneys' fees), judgments, fines and amounts paid in settlements actually and reasonably incurred by the person in connection with an action, suit or proceeding to which he or she is or is threatened to be made a party by reason of such position, if such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful, except that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnify for such expenses which the Court of Chancery or such other court shall deem proper.

Our restated certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding whether civil, criminal, administrative or investigative (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, our director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably

incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful.

Our restated certificate of incorporation also provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favor by reason of the fact that the Indemnitee is or was, or has agreed to become, our director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee or, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred by him or her or on his or her behalf in connection therewith. If we do not assume the defense, expenses must be advanced to an Indemnitee under certain circumstances.

We have entered into indemnification agreements with our directors and executive officers. In general, these agreements provide that we will indemnify the director or executive officer to the fullest extent permitted by law for claims arising in his or her capacity as a director or officer of our company or in connection with their service at our request for another corporation or entity. The indemnification agreements also provide for procedures that will apply in the event that a director or executive officer makes a claim for indemnification and establish certain presumptions that are favorable to the director or executive officer.

We maintain a general liability insurance policy that covers certain liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers.

Item 16. Exhibits

EXHIBIT NUMBER	DESCRIPTION
4.1	Restated Certificate of Incorporation of the Registrant, as amended (incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-35945) filed with the Securities and Exchange Commission on August 9, 2021)
4.2	Amended and Restated By-laws of the Registrant (incorporated by reference to the Registration Statement on Form S-1/A (File No. 333-187892) filed with the Securities and Exchange Commission on April 26, 2013)
4.3	Warrant to Purchase Stock, dated August 7, 2021, by and between the Registrant and Hutchison China MediTech Investment Limited
5.1	Opinion of WilmerHale
23.1	Consent of Ernst & Young LLP, independent registered public accounting firm for the Registrant
23.2	Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1)
24.1	Powers of Attorney (included in the signature pages to the Registration Statement)

Item 17. Undertakings.

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933, as amended (the "Securities Act");

(ii) To reflect in the prospectus any facts or events arising after the effective date of this Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this Registration Statement. Notwithstanding the foregoing, any increase or decrease in the volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective Registration Statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in this Registration Statement or any material change to such information in this Registration Statement;

provided, *however*, that paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that are incorporated by reference in this Registration Statement or is contained in a form of prospectus filed pursuant to Rule 427(b) that is part of this Registration Statement.

(2) That, for the purposes of determining any liability under the Securities Act, each post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at the time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act to any purchaser:

(i) Each prospectus filed by the Registrant pursuant to Rule 424(b)(3) shall be deemed to be part of this Registration Statement as of the date the filed prospectus was deemed part of and included in the Registration Statement; and

(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act shall be deemed to be part of and included in this Registration Statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided*, *however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of

contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

The Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the Registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in this Registration Statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the indemnification provisions described herein, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the city of Cambridge, Commonwealth of Massachusetts, on September 21, 2021.

EPIZYME, INC.

By: /s/ Grant Bogle
Grant Bogle
President and Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned officers and directors of Epizyme, Inc. hereby severally constitute and appoint Grant Bogle and Matthew Ros, and each of them singly, our true and lawful attorneys with full power to any of them, and to each of them singly, to sign for us and in our names in the capacities indicated below the Registration Statement on Form S-3 filed herewith and any and all amendments (including post-effective amendments) to said Registration Statement, and generally to do all such things in our name and on our behalf in our capacities as officers and directors to enable Epizyme, Inc. to comply with the provisions of the Securities Act of 1933, as amended, and all requirements of the Securities and Exchange Commission, hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Grant Bogle Grant Bogle	President, Chief Executive Officer and Director (Principal Executive Officer)	September 21, 2021
/s/ Matthew Ros Matthew Ros	Executive Vice President, Chief Strategy and Business Officer (Principal Financial Officer)	September 21, 2021
/s/ Joseph Beaulieu Joseph Beaulieu	Vice President, Corporate Controller and Treasurer (Principal Accounting Officer)	September 21, 2021
/s/ Andrew R. Allen Andrew R. Allen, M.D., Ph.D.	Director	September 21, 2021
/s/ Kenneth Bate Kenneth Bate	Director	September 21, 2021
/s/ Kevin T. Conroy Kevin T. Conroy	Director	September 21, 2021
/s/ Michael F. Giordano Michael F. Giordano, M.D.	Director	September 21, 2021

Signature	Title	Date
/s/ Carl Goldfischer Carl Goldfischer, M.D.	Director	September 21, 2021
/s/ Pablo Legorreta Pablo Legorreta	Director	September 21, 2021
/s/ David M. Mott David M. Mott	Director	September 21, 2021
/s/ Victoria Richon Victoria Richon, Ph.D.	Director	September 21, 2021

Execution Version

Warrant

THIS WARRANT AND THE SHARES ISSUABLE HEREUNDER HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AND PURSUANT TO THE PROVISIONS OF ARTICLE 5 BELOW, MAY NOT BE OFFERED, SOLD OR OTHERWISE TRANSFERRED, PLEDGED OR HYPOTHECATED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND APPLICABLE STATE SECURITIES LAW OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER OF THESE SECURITIES, SUCH OFFER, SALE OR TRANSFER, PLEDGE OR HYPOTHECATION IS EXEMPT FROM REGISTRATION.

WARRANT TO PURCHASE STOCK

Company:	EPIZYME, INC., a Delaware corporation (the "Company")
Class of Stock:	Common Stock of the Company, par value $0.0001 per share (the "Common Stock")
Exercise Price:	$11.50 per share
Number of Shares	5,653,000 shares of Common Stock
Issue Date:	August 7, 2021
Expiration Date:	August 7, 2025
License Agreement:	This Warrant is issued in connection with the License Agreement, dated as of August 7, 2021, by and between the Company and Hutchison China MediTech Investment Limited (as amended from time to time, the "License Agreement").

THIS WARRANT CERTIFIES THAT, for good and valuable consideration, including, without limitation, the mutual promises contained in the License Agreement, Hutchison China MediTech Investment Limited, a company incorporated in the British Virgin Islands with a company number 2031179 and a registered office of Vistra Corporate Services Centre, Wickhams Cay II, Road Town, Tortola, VG1110, British Virgin Islands ("Hutchmed," together with any registered holder from time to time of this Warrant, "Holder"), is entitled to purchase the number of fully paid and nonassessable shares of Common Stock (the "Shares") at the Exercise Price, all as set forth above and as adjusted from time to time pursuant to Article 2 of this Warrant, subject to the provisions and upon the terms and conditions set forth in this Warrant. Notwithstanding the foregoing, if Hutchmed terminates the License Agreement under Section 14.2 of the License Agreement or the Company terminates the License Agreement under Section 14.3, 14.4 or 14.6 of the License Agreement, in each case in which termination is effective prior to the Expiration Date, the number of Shares purchasable under this Warrant at the time of such termination will be decreased by 2,826,500 Shares (as adjusted pursuant to Article 2 of this Warrant), provided that if the number of Shares purchasable under this Warrant at the time of such termination is less than 2,826,500 Shares, upon such termination this Warrant shall be terminated and shall cease to be exercisable.

ARTICLE 1. EXERCISE.

1.1 Method of Exercise. Holder may exercise this Warrant in whole or in part by delivering a duly executed Notice of Exercise in substantially the form attached as Appendix 1 to the principal office of the Company, together with payment by wire transfer (to an account designated by the Company) or other form of payment acceptable to the Company for the aggregate Exercise Price of the Shares being

purchased. The date on which the later of these items is received shall be deemed the exercise date of this Warrant (unless this Warrant is exercised pursuant to Section 1.4, in which case the date of the consummation of the Acquisition (as defined below) shall be the exercise date).

1.2 Delivery of Shares and New Warrant. Promptly after the Holder exercises this Warrant under Section 1.1 and the Company receives payment of the aggregate Exercise Price in respect of such exercise, the Company shall deliver to the Holder the acquired Shares in book-entry form, and, in any event, the Holder shall be deemed to be the holder of the number of Shares for which this Warrant has been exercised upon payment of the aggregate Exercise Price. If this Warrant is surrendered in connection with the exercise and this Warrant has not been fully exercised and has not expired, the Company shall deliver to the Holder a new Warrant exercisable for the number of shares of Common Stock remaining available for purchase under this Warrant.

1.3 Replacement of Warrants. On receipt of evidence reasonably satisfactory to the Company of the loss, theft, destruction or mutilation of this Warrant and, in the case of loss, theft or destruction, on delivery of an indemnity agreement reasonably satisfactory to the Company or, in the case of mutilation on surrender and cancellation of this Warrant, the Company shall execute and deliver, in lieu of this Warrant, a new warrant of like tenor.

1.4 Treatment of Warrant Upon Acquisition of Company.

1.4.1 Treatment of Warrant at Acquisition.

(a) In the event of an Acquisition in which the consideration is cash, Marketable Securities (as defined below), or a combination thereof (the "Acquisition Consideration"), then this Warrant will be deemed to have been automatically exercised and converted immediately prior to the consummation of such Acquisition on a net basis, as described in Section 1.4.1(b); provided that if the Acquisition Consideration payable with respect to one Share is less than the Exercise Price in effect under this Warrant as of such time, then this Warrant shall not be exercised under this Section 1.4.1 and will expire immediately prior to the consummation of such Acquisition.

(b) If this Warrant is deemed to be automatically exercised pursuant to Section 1.4.1(a), the Holder shall not be required to pay the Exercise Price for the Shares and shall instead receive upon exercise of this Warrant (i) if the Acquisition Consideration payable with respect to each Share includes a cash amount in excess of the Exercise Price, the aggregate cash amount of the Acquisition Consideration for all of the Shares for which this Warrant is deemed exercised, less the aggregate Exercise Price for such Shares, plus any additional Acquisition Consideration payable for such Shares, and (ii) otherwise, the Acquisition Consideration payable for all of the Shares for which this Warrant is deemed exercised, less (A) if the Marketable Securities included in such Acquisition Consideration have an aggregate Fair Market Value equal to or greater than the aggregate Exercise Price for such Shares, the number of Marketable Securities that have a Fair Market Value equal to the aggregate Exercise Price for such Shares (rounded down to the nearest whole share of such Marketable Securities), and (B) if the Marketable Securities included in such Acquisition Consideration have an aggregate Fair Market Value that is less than the aggregate Exercise Price for such Shares, all of such Marketable Securities and a cash amount from such Acquisition Consideration equal to the amount by which the aggregate Exercise Price for such Shares exceeds the aggregate Fair Market Value of such Marketable Securities. For illustrative purposes, if (i) the Acquisition Consideration for all of the Shares consists of $100,000,000 in cash, then upon the deemed exercise, the Holder shall receive $35,000,000 in cash ($100,000,000 less the $65,000,000 aggregate Exercise Price), (ii) the Acquisition Consideration for all of the Shares consists of 5,000,000 Marketable Securities having an aggregate Fair Market Value of $100,000,000, the

Holder shall receive 1,750,000 Marketable Securities (with 3,250,000 Marketable Securities having an aggregate Fair Market Value of $65,000,000) and (iii) the Acquisition Consideration for all of the Shares consists of 2,500,000 Marketable Securities having an aggregate Fair Market Value of $50,000,000 and $50,000,000 in cash, the Holder shall receive $35,000,000 in cash (the 2,500,000 Marketable Securities having an aggregate Fair Market Value of $50,000,000 plus $15,000,000 in cash).

1.4.2 Definitions. As used in this Warrant, the following terms have the respective meanings set forth below:

(a) "Acquisition" means the (a) consolidation or merger of the Company with or into any person or entity as a result of which the outstanding voting securities or other ownership interests of the Company immediately prior to such transaction will represent fifty percent (50%) or less of the outstanding voting securities or other ownership interests of such surviving person or entity or the parent entity of such surviving person or entity immediately following such transaction, or (b) acquisition by any person or entity, or group of persons or entities acting in concert, of beneficial ownership of more than fifty percent (50%) percent of the outstanding voting securities or other ownership interests of such Party, in each case in which the holders of the shares of Common Stock of the Company then outstanding receive cash, Marketable Securities or a combination thereof in respect of their shares.

(b) "Fair Market Value" shall mean with respect to a Share or a Marketable Security, as of any particular date: (a) if such security is then listed on a Trading Market, the volume weighted average of the closing sales prices of such security averaged over twenty (20) consecutive Business Days ending on the Business Day immediately prior to the day as of which "Fair Market Value" is being determined; provided, that (i) the term "Business Day" as used in this sentence means Business Days on which such Trading Market is open for trading and (ii) if such security is not then listed or quoted on a Trading Market, the "Fair Market Value" of the Share shall be the fair market value per share as determined in good faith by the Board of Directors of the Company.

(c) "Marketable Securities" shall mean securities meeting all of the following requirements: (i) the issuer thereof is then subject to the reporting requirements of Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and is then current in its filing of all required reports and other information under the Securities Act and the Exchange Act; (ii) the class and series of shares or other security of the issuer that would be received by Holder in connection with the Acquisition were Holder to exercise this Warrant on or prior to the closing thereof is then traded on a Trading Market ; and (iii) the issuer has a market capitalization, as of the date immediately prior to and on the closing of such Acquisition of at least $1,000,000,000.

(d) "OTC Bulletin Board" shall mean the Financial Industry Regulatory Authority OTC Bulletin Board electronic inter-dealer quotation system.

(e) "Trading Market" means whichever of the New York Stock Exchange, the NYSE American (formerly the American Stock Exchange), the Nasdaq Global Select Market, the Nasdaq Global Market, the Nasdaq Capital Market or the OTC Bulletin Board is the principal market on which the Common Stock is listed or quoted for trading on the date in question.

ARTICLE 2. ADJUSTMENTS.

2.1 Stock Dividends, Splits, Etc. If the Company declares or pays a dividend on its Common Stock payable in shares of Common Stock, or other securities of the Company, then upon exercise of this Warrant, for each Share acquired, Holder shall receive, without cost to Holder, the total number and kind

of securities to which Holder would have been entitled had Holder owned the Shares of record as of the record date for the dividend. If the Company subdivides the shares of Common Stock by reclassification or otherwise into a greater number of shares, the number of Shares purchasable hereunder shall be proportionately increased and the Exercise Price shall be proportionately decreased. If the Company combines or consolidates the shares of Common Stock, by reclassification or otherwise, into a lesser number of shares, the number of Shares purchasable hereunder shall be proportionately decreased and the Exercise Price shall be proportionately increased. Any adjustment made pursuant to the first sentence of this paragraph shall become effective immediately after the record date for the determination of stockholders entitled to receive such dividend, and any adjustment pursuant to the second and third sentences of this paragraph shall become effective immediately after the effective date of such subdivision, combination or consolidation.

2.2 Reclassification, Exchange, Combinations or Substitution. In the event of any recapitalization, reclassification, exchange, substitution, combination, reorganization, merger, consolidation, liquidation or similar transaction or other event that results in the Common Stock being converted into or exchanged for securities, cash or property (other than in connection with an Acquisition that results in automatic exercise subject to Section 1.4.1), Holder shall be entitled to receive, upon exercise of this Warrant, the number and kind of securities and property that Holder would have received for the Shares if this Warrant had been exercised immediately before such event. The Company or its successor, if applicable, shall promptly issue to Holder an amendment to this Warrant setting forth the number and kind of such new securities or other property issuable upon exercise of this Warrant as a result of such event. The amendment to this Warrant shall provide for adjustments which shall be as nearly equivalent as may be practicable to the adjustments provided for in this Article 2 including, without limitation, adjustments to the Exercise Price and to the number of securities or property issuable upon exercise of the new Warrant. The provisions of this Section 2.2 shall similarly apply to successive reclassifications, exchanges, substitutions, or other events.

2.3 No Impairment. The Company shall not, by amendment of its Certificate of Incorporation or other organizational documents or through a reorganization, transfer of assets, consolidation, merger, dissolution, issuance, or sale of its securities or any other voluntary action, avoid or seek to avoid the observance or performance of any of the terms to be observed or performed under this Warrant by the Company and shall at all times in good faith assist in carrying out of all the provisions of this Article 2 and in taking all such action as may be necessary or appropriate to protect Holder's rights under this Section against impairment.

2.4 Fractional Shares. No fractional Shares shall be issuable upon exercise of this Warrant and the number of Shares to be issued shall be rounded down to the nearest whole Share. If a fractional share interest arises upon any exercise of the Warrant, the Company shall eliminate such fractional share interest by paying Holder the amount computed by multiplying the fractional interest by the Fair Market Value of a full Share.

2.5 Certificate as to Adjustments. Upon each adjustment hereunder, the Company shall promptly provide Holder with a certificate setting forth such adjustment and the facts upon which such adjustment is based, including any adjusted number of Shares exercisable hereunder and the adjusted Exercise Price.

ARTICLE 3. REPRESENTATIONS AND COVENANTS OF THE COMPANY.

3.1 Representations and Warranties. The Company represents and warrants and covenants to Holder as follows:

3.1.1 This Warrant is, and any Warrant issued in substitution for or replacement of this Warrant shall be, upon issuance, duly authorized and validly issued.

3.1.2 All Shares which may be issued upon the exercise of the purchase right represented by this Warrant, shall, upon issuance in accordance with the terms hereof, be duly authorized, validly issued, fully paid and nonassessable, free of any liens, restrictions on transfer or preemptive or similar rights imposed by the Company except for restrictions on transfer provided for herein or under applicable federal and state securities laws.

3.1.3 The Company shall take all such actions as may be necessary to ensure that all Shares are issued without violation by the Company of any applicable law or governmental regulation or the Trading Market on which the Shares are listed at the time of such exercise (except for official notice of issuance which shall be immediately delivered by the Company upon each such issuance).

3.1.4 The Company shall use its best efforts to cause the Shares, immediately upon or prior to such exercise, to be listed on the Trading Market upon which shares of Common Stock or other securities constituting Shares are listed at the time of such exercise, if any, to the extent required by the Trading Market.

3.1.5 The Company shall pay all expenses in connection with, and all issue or transfer taxes and other similar governmental charges that may be imposed on the Company with respect to, the issuance or delivery of Shares to the Holder upon exercise of this Warrant.

3.2 Notice of Certain Events. If the Company proposes at any time (a) to declare any dividend or distribution upon any of its stock, whether in cash, property, stock, or other securities and whether or not a regular cash dividend; (b) to effect any recapitalization, reclassification, exchange, substitution, reorganization, liquidation or similar transaction of any of its stock; (c) to merge, combine or consolidate with or into any other corporation, or sell, lease, license, or convey all or substantially all of its assets, or to liquidate, dissolve or wind up; or (d) liquidate the Company, then, in connection with each such event, the Company shall give Holder: (1) at least ten (10) Business Days' prior written notice of the date on which a record will be taken for such dividend, distribution, or subscription rights (and specifying the date on which the holders of Common Stock will be entitled thereto) or for determining rights to vote, if any, in respect of the matters referred to in (a) above; and (2) in the case of the matters referred to in (b) and (c) above at least ten (10) Business Days' prior written notice of the date when the same will take place (and specifying the date on which the holders of common stock will be entitled to exchange their common stock for securities or other property deliverable upon the occurrence of such event, if applicable). Notwithstanding the foregoing, the failure to deliver such notice or any defect therein shall not affect the validity of the corporate action required to be described in such notice.

3.3 Registration Rights. The Holder will be entitled to the registration rights, and the Company and Holder hereby agree to the provisions attached as Appendix 2 with respect to the registration of the Shares.

3.4 Reservation of Shares. Prior to the Expiration Date, the Company shall at all times reserve and keep available out of its authorized but unissued Common Stock or other securities constituting Shares, solely for the purpose of issuance upon the exercise of this Warrant, the maximum number of Shares issuable upon the exercise of this Warrant, and the par value per Share shall at all times be less than or equal to the applicable Exercise Price. The Company shall not increase the par value of any Shares receivable upon the exercise of this Warrant above the Exercise Price then in effect.

3.5 No Shareholder Rights. Except as provided in this Warrant, the Holder will not have any rights as a shareholder of the Company until the exercise of this Warrant.

ARTICLE 4. REPRESENTATIONS AND WARRANTIES OF THE HOLDER. The Holder represents and warrants to the Company as follows:

4.1 Purchase for Own Account. It is acquiring this warrant and the securities to be acquired upon exercise of this Warrant as of the date hereof and upon each exercise of this Warrant for investment for the Holder's account, not as a nominee or agent, and not with a view to the public resale or distribution within the meaning of the Securities Act. Holder also represents that the Holder has not been formed for the specific purpose of acquiring this Warrant or the Shares.

4.2 Disclosure of Information. The Holder has received or has had full access to all the information about the Company it considers necessary or appropriate to make an informed investment decision with respect to the acquisition of this Warrant and its underlying securities. The Holder further has had a full opportunity to ask questions and receive answers from the Company regarding the terms and conditions of the offering of this Warrant and its underlying securities and to obtain additional information (to the extent the Company possessed such information or could acquire it without unreasonable effort or expense) necessary to verify any information furnished to the Holder or to which the Holder has access.

4.3 Investment Experience. The Holder understands that the purchase of this Warrant and its underlying securities involves substantial risk. The Holder has experience as an investor in securities of companies in the development stage and acknowledges that the Holder can bear the economic risk of such Holder's investment in this Warrant and its underlying securities and has such knowledge and experience in financial or business matters that the Holder is capable of evaluating the merits and risks of its investment in this Warrant and its underlying securities.

4.4 Accredited Investor Status. The Holder is an "accredited investor" within the meaning of Regulation D promulgated under the Securities Act.

4.5 Securities Act. The Holder understands that this Warrant and the Shares issuable upon exercise hereof have not been registered under the Securities Act in reliance upon a specific exemption therefrom, which exemption depends upon, among other things, the bona fide nature of the Holder's investment intent as expressed herein. The Holder understands that this Warrant and the Shares issued upon any exercise hereof must be held indefinitely unless subsequently registered under the Securities Act and qualified under applicable state securities laws, or unless exemption from such registration and qualification are otherwise available.

ARTICLE 5. MISCELLANEOUS.

5.1 Term. This Warrant is exercisable in whole or in part at any time and from time to time on or before the Expiration Date.

5.2 Legends. This Warrant and the Shares shall be imprinted with a legend in substantially the following form:

THIS WARRANT AND THE SHARES ISSUABLE HEREUNDER HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "ACT"), OR THE SECURITIES LAWS OF ANY STATE AND, EXCEPT AS PROVIDED HEREIN, MAY NOT BE OFFERED, SOLD OR OTHERWISE TRANSFERRED, PLEDGED OR HYPOTHECATED UNLESS AND UNTIL REGISTERED UNDER SAID ACT AND APPLICABLE STATE SECURITIES LAW OR, IN THE OPINION OF LEGAL COUNSEL IN FORM AND SUBSTANCE SATISFACTORY TO THE ISSUER OF THESE SECURITIES, SUCH OFFER, SALE OR TRANSFER, PLEDGE OR HYPOTHECATION IS EXEMPT FROM REGISTRATION.

5.3 Compliance with Securities Laws on Transfer. This Warrant and the Shares issuable upon exercise of this Warrant may not be transferred or assigned in whole or in part without compliance with applicable federal and state securities laws by the transferor and the transferee (including, without

limitation, the delivery of investment representation letters and legal opinions reasonably satisfactory to the Company, as reasonably requested by the Company). The Company shall not require Holder to provide an opinion of counsel if the transfer is to any "affiliate" (as such term is defined in Regulation D promulgated under the Securities Act) of Holder, provided that any such transferee is an "accredited investor" as defined in Regulation D promulgated under the Securities Act. Additionally, the Company shall also not require an opinion of counsel if there is no material question as to the availability of current information as referenced in Rule 144(c), Holder represents that it has complied with Rule 144(d) and (e) (if applicable) in reasonable detail, the selling broker represents that it has complied with Rule 144(f) (if applicable), and the Company is provided with a copy of Holder's notice of proposed sale. The Company agrees to provide reasonable cooperation with its transfer agent and the Holder in connection with the removal of the legend referenced in Section 5.2.

5.4 Notices. All notices and other communications from the Company to the Holder, or vice versa, shall be deemed effectively given as hereinafter described (i) if given by personal delivery, then such notice shall be deemed given upon such delivery, (ii) upon delivery, if delivered by e-mail so long as the sender does not receive an automatically generated notice of delivery failure, (iii) if given by mail, then such notice shall be deemed given upon the earlier of (A) receipt of such notice by the recipient or (B) three days after such notice is deposited in first class mail, postage prepaid, and (v) if given by an internationally recognized overnight air courier, then such notice shall be deemed given one Business Day after delivery to such carrier. All notices shall be addressed to the party to be notified at the address as follows, or at such other address as such party may designate by ten days' advance written notice to the other party:

Hutchison China MediTech Investment Limited
Vistra Corporate Services Centre
Wickhams Cay II
Road Town
Tortola
VG1110
British Virgin Islands
Attention: Christian Hogg
Email: Christianh@hutch-med.com

with a copies to:

Hutchmed (China) Limited
Level 18 Metropolis Tower
10 Metropolis Drive
Hung Hom
Kowloon
Hong Kong
Attention: Christian Hogg, Director
Email: Christianh@hutch-med.com

and

Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199 USA
Attn: Marc A. Rubenstein
Email: Marc.Rubenstein@ropesgray.com

All notices to the Company shall be addressed as follows until the Holder receives notice of a change in address:

Epizyme, Inc.
400 Technology Square, Cambridge, MA 02139
Attention: General Counsel

Email:

with a copy to:

WilmerHale
60 State Street
Boston, MA 02109
Attn: Stuart Falber

Email: stuart.falber@wilmerhale.com

5.5 Amendment and Waiver. This Warrant and any term hereof may be changed, waived, discharged or terminated (either generally or in a particular instance and either retroactively or prospectively) only by an instrument in writing signed by the party against which enforcement of such change, waiver, discharge or termination is sought.

5.6 Counterparts. This Warrant may be executed in counterparts, all of which together shall constitute one and the same agreement.

5.7 Governing Law. This Warrant shall be governed by and construed in accordance with the laws of the State of Delaware, without giving effect to its principles regarding conflicts of law.

[*Signature page follows*]

IN WITNESS WHEREOF, the Parties have executed this Warrant through their duly authorized representatives to be effective as of the effective date of the License Agreement.

COMPANY:

EPIZYME, INC.

By: /s/ Robert Bazemore
Name: Robert Bazemore
Title: President & Chief Executive Officer

HOLDER:

HUTCHISON CHINA MEDITECH INVESTMENT LIMITED

By: /s/ Christian Hogg
Name: Christian Hogg
Title: Director

APPENDIX 1

NOTICE OF EXERCISE

Holder elects to purchase shares of the common stock of Epizyme, Inc. (the "Company"), par value $0.0001 per share (the "Common Stock"), pursuant to the terms of the attached Warrant, and tenders payment of the purchase price of the shares in full.

Please issue in book-entry form the shares of Common Stock in the name specified below:

Holders Name

(Address)

By its execution below and for the benefit of the Company, Holder hereby restates each of the representations and warranties in Article 4 of the Warrant as the date hereof.

HOLDER:

By: _____

Name: _____

Title: _____

(Date): _____

APPENDIX 2

REGISTRATION RIGHTS

1.1 Definitions. For the purpose of this Appendix 2:

(a) the term "***Resale Registration Statement***" shall mean any registration statement required to be filed pursuant to **Section 1.2** below, and shall include any preliminary prospectus, final prospectus, exhibit or amendment included in or relating to such registration statements;

(b) the term "***Registrable Shares***" means the Shares; *provided*, *however,* that a security shall cease to be a Registrable Share upon the earliest to occur of the following: (i) a Resale Registration Statement registering such security under the Securities Act has been declared or becomes effective and such security has been sold or otherwise transferred by Holder pursuant to and in a manner contemplated by such effective Resale Registration Statement, (ii) such security is sold pursuant to Rule 144 under the Securities Act under circumstances in which any legend borne by such security relating to restrictions on transferability thereof, under the Securities Act or otherwise, is removed by the Company, (iii) such security is 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 Holder complying with any method of sale requirements or notice requirements under Rule 144 under the Securities Act, or (iv) such security shall cease to be outstanding following its issuance; and

(c) all other terms that are capitalized but not otherwise defined in this Appendix 2 shall have the meaning given them in the Warrant to which this Appendix 2 is attached.

1.2 Registration Procedures and Expenses. The Company shall:

(a) file a Resale Registration Statement (the "***Mandatory Registration Statement***") with the Securities and Exchange Commission (the "***Commission***") on or before September 21, 2021 (the "***Filing Date***") to register all of the Registrable Shares on Form S-3 under the Securities Act (providing for shelf registration of such Registrable Shares under Rule 415 of the Securities Act). In the event that Form S-3 is not available for the registration of the Registrable Shares, the Company shall register the resale of the Registrable Shares on such other form as is available to the Company;

(b) use its commercially reasonable efforts to cause such Mandatory Registration Statement to be declared effective as soon as practicable and in any event within the earlier of: (i) 30 days following the Filing Date and (ii) five Business Days after the date the Company receives written notification from the Commission that the Mandatory Registration Statement will not be reviewed; *provided*, *however*, that in the event the Staff reviews and has written comments to the Mandatory Registration Statement, such time period shall be within 90 days following the Filing Date (the earlier of the foregoing or the applicable date set forth in **Section 1.2(i)**, the "***Effectiveness Deadline***"), such efforts to include, without limiting the generality of the foregoing, preparing and filing with the Commission any financial statements or other information that is required to be filed prior to the effectiveness of such Mandatory Registration Statement;

(c) notwithstanding anything contained in this Agreement to the contrary, in the event that the Commission limits the amount of Registrable Shares or otherwise requires a reduction in the number of Registrable Shares that may be included and sold by Holder in the Mandatory Registration Statement, then the Company shall prepare and file (i) within 20 days of the first date or time that such excluded Registrable Shares may then be included in a Resale Registration Statement if the Commission shall have notified the Company that certain Registrable Shares were not eligible for inclusion in the Resale Registration Statement or (ii) in all other cases, within 20 days following the date that the Company becomes aware that such additional Resale Registration Statement is required (the "***Additional Filing Date***"), a Resale Registration Statement (any such Resale Registration Statement registering such excluded Registrable Shares, an "***Additional Registration Statement***" and, together with the Mandatory Registration Statement, a "***Resale Registration Statement***") to register any Registrable Shares that have been excluded (or, if applicable, the maximum number of such excluded Registrable Shares that the Company is permitted to register for resale on such Additional Registration Statement consistent with Commission guidance), if any, from being registered on the Mandatory Registration Statement;

(d) not less than two (2) Business Days prior to the filing of a Registration Statement or any related prospectus or any amendment or supplement thereto, furnish via email to Holder copies of all such documents proposed to be filed, which documents (other than any document that is incorporated or deemed to be incorporated by reference therein) will be subject to the reasonable review of Holder. The Company shall reflect in each such document when so filed with the Commission such comments regarding Holder and the plan of distribution as Holder may reasonably and promptly propose no later than two (2) Business Days after Holder have been so furnished with copies of such documents.

(e) use its commercially reasonable efforts to cause any such Additional Registration Statement to be declared effective as promptly as practicable following the Additional Filing Date, such efforts to include, without limiting the generality of the foregoing, preparing and filing with the Commission any financial statements or other information that is required to be filed prior to the effectiveness of any such Additional Registration Statement;

(f) promptly prepare and file with the Commission such amendments and supplements to such Resale Registration Statements and the prospectus used in connection therewith as may be necessary to keep such Resale Registration Statements continuously effective and free from any material misstatement or omission to state a material fact therein until termination of such obligation as provided in **Section 1.6** below, subject to the Company's right to suspend pursuant to **Section 1.5**;

(g) furnish to Holder such number of copies of prospectuses in conformity with the requirements of the Securities Act and such other documents as Holder may reasonably request, in order to facilitate the public sale or other disposition of all or any of the Registrable Shares by Holder;

(h) file such documents as may be required of the Company for normal securities law clearance for the resale of the Registrable Shares in such states of the United States as may be reasonably requested by Holder and use its commercially reasonable efforts to maintain such blue sky qualifications during the period the Company is required to maintain effectiveness of the Resale Registration Statements; *provided, however,* that the Company shall not be required in connection with this **Section 1.2(h)** to qualify as a foreign corporation, subject itself to general taxation or execute a general consent to service of process in any jurisdiction in which it is not now so qualified or has not so consented;

(i) upon notification by the Commission that the Resale Registration Statement will not be reviewed or is not subject to further review by the Commission, the Company shall within three Business Days following the date of such notification request acceleration of such Resale Registration Statement (with the requested effectiveness date to be not more than two Business Days later);

(j) upon notification by the Commission that that the Resale Registration Statement has been declared effective by the Commission, the Company shall file the final prospectus under Rule 424 of the Securities Act ("***Rule 424***") within the applicable time period prescribed by Rule 424;

(k) advise Holder promptly (and in any event within two (2) Business Days thereof):

(i) of the effectiveness of the Resale Registration Statement or any post-effective amendments thereto;

(ii) of any request by the Commission for amendments to the Resale Registration Statement or amendments to the prospectus or for additional information relating thereto;

(iii) of the issuance by the Commission of any stop order suspending the effectiveness of the Resale Registration Statement under the Securities Act or of the suspension by any state securities commission of the qualification of the Registrable Shares for offering or sale in any jurisdiction, or the initiation of any proceeding for any of the preceding purposes; and

(iv) of the existence of any fact and the happening of any event that makes any statement of a material fact made in the Resale Registration Statement, the prospectus and amendment or supplement thereto, or any document incorporated by reference therein, untrue, or that requires the making of any additions to or changes in the Resale Registration Statement or the prospectus in order to make the statements therein not misleading;

(l) cause all Registrable Shares to be listed on each securities exchange, if any, on which equity securities by the Company are then listed; and

(m) bear all expenses in connection with the procedures in paragraphs (a) through (l) of this **Section 1.2** and the registration of the Registrable Shares on such Resale Registration Statement and the satisfaction of the blue sky laws of such states.

1.3 Rule 415; Cutback.

If at any time the staff of the Commission ("***Staff***") takes the position that the offering of some or all of the Registrable Shares in a Registration Statement is not eligible to be made on a delayed or continuous basis under the provisions of Rule 415 under the Securities Act or requires Holder to be named as an "underwriter," the Company shall (in consultation with legal counsel to Holder) use its commercially reasonable efforts to persuade the Commission that the offering contemplated by the Registration Statement is a valid secondary offering and not an offering "by or on behalf of the issuer" as defined in Rule 415 and that Holder is not an "underwriter." In the event that, despite the Company's commercially reasonable efforts and compliance with the terms of this **Section 1.3**, the Staff refuses to alter its position, the Company shall (i) remove from the Registration Statement such portion of the Registrable Shares (the "***Cut Back Shares***") and/or (ii) agree to such restrictions and limitations on the registration and resale of the Registrable Shares as the Staff may require to assure the Company's compliance with the requirements of Rule 415 (collectively, the "***SEC Restrictions***"); *provided, however*, that the Company shall not agree to name Holder as an "underwriter" in such Registration Statement without the prior written consent of Holder.

1.4 Indemnification.

(a) The Company agrees to indemnify and hold harmless Holder and its affiliates, officers, directors, agents and representatives, and each person, if any, who controls Holder within the meaning of Section 15 of the Securities Act or Section 20 the Exchange Act (each, a "***Holder Party***" and collectively the "***Holder Parties***"), to the fullest extent permitted by applicable law, from and against any losses, claims, damages or liabilities (collectively, "***Losses***") to which the Holder Parties may become subject (under the Securities Act or otherwise), insofar as such Losses (or actions or proceedings in respect thereof) arise out of, or are based upon, any material breach of this Agreement by the Company or any untrue statement or alleged untrue statement of a material fact contained in the Resale Registration Statement or any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading or arise out of any failure by the Company to fulfill any undertaking included in the Resale Registration Statement and the Company will, as incurred, reimburse Holder Parties for any reasonable and documented legal or other expenses reasonably incurred in investigating, defending or preparing to defend any such action, proceeding or claim; *provided, however,* that the Company shall not be liable in any such case to the extent that such Loss arises out of, or is based upon: (i) an untrue statement or omission or alleged untrue statement or omission made in such Resale Registration Statement in reliance upon and in conformity with written information furnished to the Company by or on behalf of Holder specifically for use in preparation of the Resale Registration Statement; or (ii) any breach of this Agreement by Holder; *provided further, however,* that the Company shall not be liable to any Holder Party (or any officer, director or controlling person of Holder) to the extent that any such Loss is caused by an untrue statement or omission or alleged untrue statement or omission made in any preliminary

prospectus if either (i) (A) Holder failed to send or deliver a copy of the final prospectus with or prior to, or Holder failed to confirm that a final prospectus was deemed to be delivered prior to (in accordance with Rule 172 of the Securities Act), the delivery of written confirmation of the sale by Holder to the person asserting the claim from which such Loss resulted and (B) the final prospectus corrected such untrue statement or omission or (ii) (X) such untrue statement or omission is corrected in an amendment or supplement to the prospectus and (Y) having previously been furnished by or on behalf of the Company with copies of the prospectus as so amended or supplemented or notified by the Company that such amended or supplemented prospectus has been filed with the Commission, in accordance with Rule 172 of the Securities Act, Holder thereafter fails to deliver such prospectus as so amended or supplemented, with or prior to or Holder fails to confirm that the prospectus as so amended or supplemented was deemed to be delivered prior to (in accordance with Rule 172 of the Securities Act), the delivery of written confirmation of the sale by Holder to the person asserting the claim from which such Loss resulted.

(b) Holder agrees to indemnify and hold harmless the Company and its officers, directors, affiliates, agents and representatives and each person, if any, who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act (each a "***Company Party***" and collectively the "***Company Parties***"), from and against any Losses to which the Company Parties may become subject (under the Securities Act or otherwise), insofar as such Losses (or actions or proceedings in respect thereof) arise out of, or are based upon, any material breach of this Agreement by Holder or any untrue statement or alleged untrue statement of a material fact contained in the Resale Registration Statement or any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading, in each case, on the effective date thereof, if, and only to the extent, such untrue statement or omission or alleged untrue statement or omission was made in reliance upon and in conformity with written information furnished by or on behalf of Holder specifically for use in preparation of the Resale Registration Statement, and Holder will reimburse each Company Party for any reasonable and documented legal or other expenses reasonably incurred in investigating, defending or preparing to defend any such action, proceeding or claim; *provided*, *however*, that, except to the extent that any such losses, claims, damages or liabilities are finally judicially determined to have resulted from Holder's bad faith, gross negligence, recklessness, fraud or willful misconduct, in no event shall any indemnity under this **Section 1.4(b)** be greater in amount than the dollar amount of the net proceeds received by Holder upon its sale of the Registrable Shares included in the Registration Statement giving rise to such indemnification obligation.

(c) Promptly after receipt by any indemnified person of a notice of a claim or the beginning of any action in respect of which indemnity is to be sought against an indemnifying person pursuant to this **Section 1.4**, such indemnified person shall notify the indemnifying person in writing of such claim or of the commencement of such action, and, subject to the provisions hereinafter stated, in case any such action shall be brought against an indemnified person and such indemnifying person shall have been notified thereof, such indemnifying person shall be entitled to participate therein, and, to the extent that it shall wish, to assume the defense thereof, with counsel reasonably satisfactory to such indemnified person.

After notice from the indemnifying person to such indemnified person of its election to assume the defense thereof, such indemnifying person shall not be liable to such indemnified person for any legal expenses subsequently incurred by such indemnified person in connection with the defense thereof; *provided, however,* that if there exists or shall exist a conflict of interest that would make it inappropriate in the reasonable judgment of the indemnified person for the same counsel to represent both the indemnified person and such indemnifying person or any affiliate or associate thereof, the indemnified person shall be entitled to retain its own counsel at the expense of such indemnifying person; *provided, further*, that no indemnifying person shall be responsible for the fees and expense of more than one separate counsel for all indemnified parties. The indemnifying party shall not settle an action without the consent of the indemnified party, which consent shall not be unreasonably withheld. The indemnifying party shall not, except with the consent of the indemnified party, which shall not be unreasonably withheld or conditioned, consent to entry of any judgment or enter into any settlement that does not include as an unconditional term thereof the giving by the claimant or plaintiff to such indemnified party of a release from all liability in respect of such claim or litigation.

(d) If after proper notice of a claim or the commencement of any action against the indemnified party, the indemnifying party does not choose to participate, then the indemnified party shall assume the defense thereof and upon written notice by the indemnified party requesting advance payment of a stated amount for its reasonable defense costs and expenses, the indemnifying party shall advance payment for such reasonable defense costs and expenses (the "***Advance Indemnification Payment***") to the indemnified party. In the event that the indemnified party's actual defense costs and expenses exceed the amount of the Advance Indemnification Payment, then upon written request by the indemnified party, the indemnifying party shall reimburse the indemnified party for such difference; in the event that the Advance Indemnification Payment exceeds the indemnified party's actual costs and expenses, the indemnified party shall promptly remit payment of such difference to the indemnifying party.

(e) If the indemnification provided for in this **Section 1.4** is held by a court of competent jurisdiction to be unavailable to an indemnified party with respect to any losses, claims, damages or liabilities referred to herein, the indemnifying party, in lieu of indemnifying such indemnified party thereunder, shall to the extent permitted by applicable law contribute to the amount paid or payable by such indemnified party as a result of such loss, claim, damage or liability in such proportion as is appropriate to reflect the relative fault of the indemnifying party on the one hand and of the indemnified party on the other, as well as any other relevant equitable considerations; *provided*, that, except to the extent that any such losses, claims, damages or liabilities are finally judicially determined to have resulted from an indemnifying party's bad faith, gross negligence, recklessness, fraud or willful misconduct, in no event shall any contribution by an indemnifying party hereunder be greater in amount than the dollar amount of the proceeds received by such indemnifying party upon the sale of such Registrable Shares.

1.5 Prospectus Suspension. Holder acknowledges that there may be times when the Company must suspend the use of the prospectus forming a part of the Resale Registration Statement until such time as an amendment to the Resale Registration Statement has been filed by the Company and declared effective by the Commission, or until such time as the Company has filed an appropriate report with the Commission pursuant to the Exchange Act. The

Company may suspend the use of the prospectus forming a part of the Resale Registration Statement (1) upon issuance by the Commission of a stop order suspending the effectiveness of the Resale Registration Statement or the initiation of proceedings with respect to such registration statement under Section 8(d) or 8(e) of the Securities Act, or (2) if the Company determines in its sole discretion that such suspension is necessary to delay the disclosure of material information concerning the Company, the disclosure of which at the time is not in the Company's best interests. Holder hereby covenants that it will not sell any Registrable Shares pursuant to said prospectus during the period commencing at the time at which the Company gives Holder notice of the suspension of the use of said prospectus and ending at the time the Company gives Holder notice that Holder may thereafter effect sales pursuant to said prospectus; *provided*, that such suspension periods shall in no event exceed 60 days in any 12 month period.

1.6 Termination of Obligations. The obligations of the Company pursuant to **Section 1.2** hereof shall cease and terminate, with respect to any Registrable Shares, upon the earlier to occur of (a) such time such Registrable Shares have been resold, or (b) such time as such Registrable Shares no longer remain Registrable Shares pursuant to **Section 1.1(b)** hereof.

1.7 Reporting Requirements.

(a) With a view to making available the benefits of certain rules and regulations of the Commission that may at any time permit the sale of the Shares to the public without registration or pursuant to a registration statement on Form S-3, the Company agrees to use:

(i) make and keep public information available, as those terms are understood and defined in Rule 144 under the Securities Act;

(ii) file with the Commission in a timely manner all reports and other documents required of the Company under the Exchange Act; and

(iii) so long as Holder owns Registrable Shares, to furnish to Holder upon request (A) a written statement by the Company as to whether it is in compliance with the reporting requirements of the Exchange Act, (B) a copy of the most recent annual or quarterly report of the Company and such other reports and documents so filed by the Company (provided that the Company's obligations to provide such copies shall be deemed satisfied by filing the same with the Commission pursuant to the Electronic Data Gathering Analysis and Retrieval System) and (C) such other information as may be reasonably requested to permit Holder to sell such securities pursuant to Rule 144 under the Securities Act.

Exhibit 5.1

WILMERHALE

+1 617 526 6000 (t)
+1 617 526 5000 (f)
wilmerhale.com

September 21, 2021

Epizyme, Inc.
400 Technology Square, 4th Floor
Cambridge, Massachusetts 02139

Re: Registration Statement on Form S-3

Ladies and Gentlemen:

This opinion is furnished to you in connection with a Registration Statement on Form S-3 (the "Registration Statement") filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), for the registration of an aggregate of 5,653,000 shares of Common Stock, $0.0001 par value per share (the "Shares"), of Epizyme, Inc., a Delaware corporation (the "Company"). All of the Shares are being registered on behalf of a certain stockholder of the Company (the "Selling Stockholder") and are issuable upon the exercise of a warrant that is held by the Selling Stockholder (the "Warrant").

We are acting as counsel for the Company in connection with the registration for resale of the Shares. We have examined signed copies of the Registration Statement filed with the Commission. We have also examined and relied upon minutes of meetings of the stockholders and the Board of Directors of the Company as provided to us by the Company, stock record books of the Company as provided to us by the Company, the Restated Certificate of Incorporation and Amended and Restated Bylaws of the Company, each as restated and/or amended to date, and such other documents as we have deemed necessary for purposes of rendering the opinions hereinafter set forth.

In our examination of the foregoing documents, we have assumed the genuineness of all signatures, the authenticity of all documents submitted to us as originals, the conformity to original documents of all documents submitted to us as copies, the authenticity of the originals of such latter documents and the legal competence of all signatories to such documents.

We assume that the appropriate action will be taken, prior to the offer and sale of the Shares, to register and qualify the Shares for sale under all applicable state securities or "blue sky" laws.

We express no opinion herein as to the laws of any state or jurisdiction other than the state laws of the Commonwealth of Massachusetts and the General Corporation Law of the State of Delaware and the federal laws of the United States of America.

Based upon and subject to the foregoing, we are of the opinion that the Shares have been duly authorized and the Shares will be, when issued, delivered and paid for in accordance with the terms of the Warrant, validly issued, fully paid and nonassessable.

It is understood that this opinion is to be used only in connection with the offer and sale of the Shares while the Registration Statement is in effect.

Please note that we are opining only as to the matters expressly set forth herein, and no opinion should be inferred as to any other matters. This opinion is based upon currently existing statutes, rules, regulations and judicial decisions, and we disclaim any obligation to advise you of any change in any of these sources of law or subsequent legal or factual developments which might affect any matters or opinions set forth herein.

We hereby consent to the filing of this opinion with the Commission as an exhibit to the Registration Statement in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Securities Act and to the use of our name therein and in the related prospectus under the caption "Legal Matters." In giving such consent, we do not hereby admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission.

Very truly yours,

WILMER CUTLER PICKERING
HALE AND DORR LLP

By: /s/ Stuart M. Falber
Stuart M. Falber, a Partner

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption “Experts” in the Registration Statement (Form S-3) and related Prospectus of Epizyme, Inc. for the registration of 5,653,000 shares of its common stock and to the incorporation by reference therein of our reports dated February 23, 2021, with respect to the consolidated financial statements of Epizyme, Inc., and the effectiveness of internal control over financial reporting of Epizyme, Inc., included in its Annual Report (Form 10-K) for the year ended December 31, 2020, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Boston, Massachusetts
September 21, 2021