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

DIVISION OF
CORPORATION FINANCE

April 19, 2013

Via E-Mail
Jason Rhodes
Executive Vice President and Chief Financial Officer
Epizyme, Inc.
400 Technology Square
Cambridge, MA 02139

Re: Epizyme, Inc.
Registration Statement on Form S-1
Filed April 18, 2013
File No. 333-187982

Dear Mr. Rhodes:

We have reviewed your registration statement and have the following comments. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure.

Please respond to this letter by amending your registration statement and providing the requested information. If you do not believe our comments apply to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing any amendment to your registration statement and the information you provide in response to these comments, we may have additional comments.

General

1. Please note that where we provide examples or references to portions of your filing to illustrate what we mean by our comments, they are examples and not exhaustive lists. If our comments are applicable to portions of the filings that we have not cited as examples, please make the appropriate changes elsewhere in the filing in accordance with our comments.

2. Please submit all exhibits as soon as practicable. We may have further comments upon examination of these exhibits.

3. Please confirm that the graphics included in your registration statement are the only graphics you will use in your prospectus. If you will use any additional graphic, visual or photographic information in the printed prospectus, please provide us a proof of each

such item for our review prior to its use. Please note that we may have comments regarding this material.

4. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications. Similarly, please supplementally provide us with any research reports about you that are published or distributed in reliance upon Section 2(a)(3) of the Securities Act of 1933 added by Section 105(a) of the Jumpstart Our Business Startups Act by any broker or dealer that is participating or will participate in your offering.

5. We note that you submitted a confidential treatment request on March 25, 2013. We will provide any comments in relation to your confidential treatment request in a separate comment letter.

Summary, page 1

Our Strategy, page 2

6. We note your reference to the expedited regulatory approval obtained by Zelboraf and Xalkori in 2011. Please revise your disclosure to indicate why you believe that your product candidates may be able to rely on a similarly expedited regulatory approval process. In the interest of balanced disclosure, please also revise your prospectus summary to highlight that there is significant uncertainty that your product candidates will obtain regulatory approval and that, in any event, your product candidates may not qualify for the fast-track designation, expedited review, or accelerated approval process relied upon by Zalboraf and Xalkori.

7. Please define the term oral bioavailabilty as used in reference to the Phase 1/2 clinical trial for EPZ-6438.

Risks Associated with Our Business, page 5

8. Please revise your disclosure to quantify the extent of losses you have incurred since inception in your prospectus summary.

9. Please revise your risk discussion to highlight that the scientific evidence supporting the feasibility of your product candidates is both preliminary and limited. In addition, please also note that no other companies have conducted clinical trials of HMT inhibitors.

Risk Factors, page 11

"If we fail to comply with our obligations in our intellectual property licenses…" page 27

10. You state that your licensing and funding arrangements may impose certain obligations on you. Please revise your disclosure to clarify that you are currently subject to various obligations under your licensing and funding arrangements and briefly summarize these obligations in your risk factor.

Use of Proceeds, page 42

11. Please expand your disclosure to indicate the approximate amount of proceeds you intend to use for each indicated purpose.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Collaborations, page 49

12. Please disclose the aggregate amount of milestone-based development payments associated with the Abbott agreement. This also applies to your disclosure on page F-32.

Stock-Based Compensation, page 53

13. We have reviewed your stock-based compensation disclosures and have the following comments:
    - We note that you used an assumed cost of capital of 19 – 20% at each valuation date. Please tell us, and disclose the source used to determine the assumed cost of capital at each period.
    - Disclose how you determined the weighting given to no value to common for each valuation.
    - Please update the table on page 54 through the date of the amendment.
    - Please note we may have additional comments on your accounting for stock compensation and related disclosure once you have disclosed an estimated offering price. Please provide quantitative and qualitative disclosures explaining the difference between the estimated offering price and the fair value of each equity issuance.

Financial Overview and Results of Operations for the Years Ended December 31, 2011 and 2012
Research and Development, page 60

14. Please disclose the total costs incurred to date for EPZ-5676 and EPZ-6438, respectively.

Business, page 66

EPZ-5676—DOT1L Inhibitor—
Phase 1 Clinical Trial, page 73

15. You state that the Phase 1 trial is not powered to show results with statistical significance. Please expand your disclosure to discuss the reliability of your results in light of this limitation.

Preclinical Studies, page 73

16. Please expand your disclosure to clarify:
    - the number of subjects in the vehicle and dose 2 groups; and
    - the number of subject in the dose 2 group that experienced tumor stasis of up to seven days past the discontinuation of drug treatment.

    Please also revise your chart to clarify that the subjects in the dose 2 group received 35 mg/kg per day of EPZ-5676, not 25 mg/kg.

EPZ-6438—EZH2 Inhibitor
Planned Phase 1/2 Clinical Trial, page 75

17. You state that neither of these clinical trials will be powered to show results with statistical significance. Please expand your disclosure to discuss the reliability of your results in light of this limitation.

Preclinical Studies, page 76

18. Please expand your disclosure to clarify the number of subjects in the three subject groups.

HMT Collaborations, page 77

19. In your discussion of each of the Celgene, Eisai, and GSK agreements, please clarify the term of the agreement by specifying the minimum number of years following the first commercial sale after which the royalty term for a given product expires. We note that you have requested confidential treatment for this information in the agreements cited. However, the duration of an agreement represents material information necessary for an investor's understanding of the agreement's terms and obligations. Because the duration of the royalty obligation is directly related to the term of these agreements, we would also view this as material information which must be disclosed in the registration statement. Please revise your disclosure accordingly.

Eisai, page 79

20. In your description of your agreement with Eisai on page 79, you state that you received $9.5 million in research funding, but on page F-23, you state that you recorded $11.3 million. Please reconcile these statements.

GlaxoSmithKline, page 80

21. Please revise your disclosure to describe the circumstances in which you could be required to pay royalties to GSK based on annual net sales of your products. Please also provide an estimate of the range of royalties you may be required to pay within a 10% range.

Abbott, page 81

22. Please expand your description of your agreement with Abbott to include:
    - the amount of the upfront payment; and
    - the aggregate milestone payments to be made over the term of the agreement.

    We note that you have requested confidential treatment for the individual milestone-based payments that you may be required to pay Abbott. In this regard, please note that our comment requests disclosure of potential milestone obligations on an aggregate basis, not on an individual basis.

Roche, page 81

23. Please expand your description of your agreement with Roche to include:
    - the amount that Eisai will be entitled to deduct from future royalties to you as a result of its funding payments to Roche; and
    - the aggregate potential milestones that may be paid to Roche and the pro rata amount of such milestone payments that you may become obligated to fund.

    We note that you have requested confidential treatment for the individual milestone-based payments that you may be required to pay Roche. In this regard, please note that our comment requests disclosure of potential milestone obligations on an aggregate basis, not on an individual basis.

UNC In-Licensed Portfolio, page 84

24. Please expand your description of your agreement with UNC to disclose:
    - payments made to date;
    - the range of potential royalties you may be obligated to pay on net product sales of screening method technologies and related products;
    - the duration of the agreement; and
    - any termination provisions.

In addition, you state that the royalties payable to UNC do not relate to your current product candidates. Please clarify whether, and if so, how, the intellectual property you have licensed from UNC relates to your current product candidates.

Description of Capital Stock, page 122

25. Please expand your disclosure to include the approximate number of holders of each class of common equity of the registrant as of the latest practicable date.

26. Please expand your disclosure to indicate the voting threshold for matters besides election of directors that may be voted on by holders of shares of your common.

7. Redeemable Convertible Preferred Stock
Conversion, page F-17

27. You indicate that the preferred shares are subject to certain antidilution adjustments, such as upon certain defined dilutive issuances of common stock or common stock equivalents. Please clarify for us and in your disclosure the nature all the antidilution adjustments associated with your preferred shares, and the accounting impact, if any such adjustments have or will have on your shares.

9. Collaborations, page F-20

28. For each of your agreements, please provide the inputs, assumptions, and methods used to determine the relative selling price, as required under ASC 605-25-50-2e. The current disclosures solely address the factors considered in your analysis.

29. Your current disclosure aggregates the development and regulatory milestone payments associated with your agreements with Celgene, Eisai and GlaxoSmithKline. Please revise your disclosure to describe each substantive milestone and the related contingent consideration. Refer to ASC 605-28-50-2b.

30. For each of your agreements, please clarify whether there are any joint steering committees, and if so, why you concluded that they were not deliverables and revise your disclosure as necessary.

31. With respect to your agreements with Celgene and Eisai, you indicate that the licenses do not have standalone value apart from the related research services due to the limited economic benefit that these parties would derive if they did not obtain the research services. Please clarify what is meant by “limited economic benefit”, and address whether the license has value on a standalone basis using the criteria described in ASC 605-25-25-5a.

32. Please tell us why you concluded it is appropriate to distinguish that the post IND research services have been accounted for as separate units of accounting which have standalone value upon delivery, and why such services are not combined with the research services provided before IND effectiveness.

33. With respect to the Celgene agreement, you indicate that there is no contractual limit to the number of licenses to available targets, and that the number of selected targets is not known. Please tell us how you determined the option exercise fee included in the total allocable arrangement consideration is fixed and determinable and disclose such amount Refer to ASC 605-25-30-1.

34. With respect to your remaining DOT1L research services in which you determined that there were two separate units of accounting, please address the following:
    - Quantitatively disclose the estimated period in which you are recognizing revenue for each unit of accounting.
    - Tell us why the estimated revenue recognition periods are ending at the completion of the of the Phase 1 clinical trial for the first and estimated IND effectiveness for the second.
    - Revise your disclosure to clarify what performance obligation you have after the above events occur. Your disclosure in the last paragraph of page F-20 implies that you will be continuing to develop candidates after the events.

Item 16. Exhibits and Financial Statement Schedules, page II-3

35. Please file the form of lock-up agreement as an exhibit to your registration statement.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that the filing includes the information the Securities Act of 1933 and all applicable Securities Act rules require. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

Notwithstanding our comments, in the event you request acceleration of the effective date of the pending registration statement please provide a written statement from the company acknowledging that:

- should the Commission or the staff, acting pursuant to delegated authority, declare the filing effective, it does not foreclose the Commission from taking any action with respect to the filing;

- the action of the Commission or the staff, acting pursuant to delegated authority, in declaring the filing effective, does not relieve the company from its full responsibility for the adequacy and accuracy of the disclosure in the filing; and

- the company may not assert staff comments and the declaration of effectiveness as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

Please refer to Rules 460 and 461 regarding requests for acceleration. We will consider a written request for acceleration of the effective date of the registration statement as confirmation of the fact that those requesting acceleration are aware of their respective responsibilities under the Securities Act of 1933 and the Securities Exchange Act of 1934 as they relate to the proposed public offering of the securities specified in the above registration statement. Please allow adequate time for us to review any amendment prior to the requested effective date of the registration statement.

You may contact Tabatha Akins at (202) 551-3658 or Joel Parker at (202) 551-3651 if you have questions regarding comments on the financial statements and related matters. Please contact Amy Reischauer at (202) 551-3793, Bryan Pitko at (202) 551-3203, or me at (202) 551-3715 with any other questions.

Sincerely,

/s/ Jeffrey P. Riedler

Jeffrey P. Riedler
Assistant Director

cc: Via E-Mail
Rosemary Reilly
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109