

PUMA BIOTECHNOLOGY, INC.
Form 424B5
January 20, 2015
Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-201603

The information in this preliminary prospectus supplement is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and we are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion

Preliminary Prospectus Supplement dated January 20, 2015

PROSPECTUS SUPPLEMENT

(To prospectus dated January 20, 2015)

1,000,000 Shares

Puma Biotechnology, Inc.

Common Stock

We are selling 1,000,000 shares of our common stock.

Our shares trade on the New York Stock Exchange under the symbol **PBYI**. On January 16, 2015, the last reported sale price of the shares as reported on the New York Stock Exchange was \$215.52 per share.

Investing in our common stock involves risks that are described in the Risk Factors section beginning on page S-7 of this prospectus supplement.

	Per Share	Total
Public offering price	\$	\$
Underwriting discount (1)	\$	\$
Proceeds, before expenses, to us	\$	\$

(1) See Underwriting for additional disclosure regarding underwriting discounts, commissions and estimated offering expenses.

The underwriters may also exercise their option to purchase up to an additional 150,000 shares from us, at the public offering price, less the underwriting discount, for 30 days after the date of this prospectus supplement.

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 shares will be ready for delivery on or about _____, 2015.

BofA Merrill Lynch
Leerink Partners

J.P. Morgan

Citigroup
Cowen and Company

The date of this prospectus supplement is _____, 2015.

Table of Contents

TABLE OF CONTENTS
PROSPECTUS SUPPLEMENT

	Page
<u>ABOUT THIS PROSPECTUS SUPPLEMENT</u>	S-ii
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-1
<u>RISK FACTORS</u>	S-7
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	S-9
<u>USE OF PROCEEDS</u>	S-10
<u>PRICE RANGE OF COMMON STOCK</u>	S-11
<u>DIVIDEND POLICY</u>	S-11
<u>DILUTION</u>	S-12
<u>MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS</u>	S-14
<u>UNDERWRITING</u>	S-18
<u>LEGAL MATTERS</u>	S-25
<u>EXPERTS</u>	S-25
<u>WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE</u>	S-25
ACCOMPANYING PROSPECTUS	

ABOUT THIS PROSPECTUS	1
WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE	2
THE COMPANY	4
RISK FACTORS	5
USE OF PROCEEDS	6
RATIO OF EARNINGS TO FIXED CHARGES	7
DESCRIPTION OF CAPITAL STOCK	8
DESCRIPTION OF DEBT SECURITIES	11
DESCRIPTION OF OTHER SECURITIES	19
GLOBAL SECURITIES	20
PLAN OF DISTRIBUTION	23
LEGAL MATTERS	24
EXPERTS	24

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is the prospectus supplement, including the documents incorporated by reference, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. Before you invest, you should carefully read this prospectus supplement, the accompanying prospectus, all information incorporated by reference herein and therein, as well as the additional information described under **Where You Can Find More Information; Incorporation by Reference** on page S-25 of this prospectus supplement. These documents contain information you should consider when making your investment decision. This prospectus supplement may add, update or change information contained in the accompanying prospectus. To the extent that any statement that we make in this prospectus supplement is inconsistent with statements made in the accompanying prospectus or any documents incorporated by reference, the statements made in this prospectus supplement will be deemed to modify or supersede those made in the accompanying prospectus and such documents incorporated by reference.

You should rely only on the information contained or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectuses we may provide to you in connection with this offering. Neither we nor any of the underwriters have authorized any other person to provide you with any information that is different. If anyone provides you with different or inconsistent information, you should not rely on it. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement outside the United States. This prospectus supplement does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise indicated, information contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference, concerning our industry and the markets in which we operate, including our general expectations and market position, market opportunity and market share, is based on information from our own management estimates and research, as well as from industry and general publications and research, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry and assumptions based on such information and knowledge, which we believe to be reasonable. In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in **Risk Factors** in this prospectus supplement, the accompanying prospectus and in our Annual Report on Form 10-K for the fiscal year ended December 31, 2013, which are incorporated by reference into this prospectus supplement. These and other important factors could cause our future performance to differ materially from our assumptions and estimates. See **Special Note Regarding Forward-Looking Statements**.

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information about us, this offering and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all of the information you should consider before investing in our common stock pursuant to this prospectus supplement and the accompanying prospectus. Before making an investment decision, to fully understand this offering and its consequences to you, you should carefully read this entire prospectus supplement and the accompanying prospectus, including Risk Factors beginning on page S-7 of this prospectus supplement, the financial statements and related notes, and the other information that we incorporate by reference into this prospectus supplement, including the section Risk Factors in our Annual Report on Form 10-K for the fiscal year ended December 31, 2013. As used in this prospectus supplement, unless the context requires otherwise, the terms Company, we, our and us refer to Puma Biotechnology, Inc. together with our wholly-owned subsidiary, Puma Biotechnology Ltd.

Our Company

We are a development stage biopharmaceutical company with a focus on the acquisition, development and commercialization of innovative products to enhance cancer care. We aim to acquire proprietary rights to these products, by license or otherwise, fund their research and development and bring the products to market. Our efforts and resources to date have been focused primarily on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel.

We currently license the rights to three drug candidates:

PB272 (neratinib (oral)), which we are developing for the treatment of patients with human epidermal growth factor receptor type 2, or HER2, positive breast cancer, and patients with non-small cell lung cancer, breast cancer and other solid tumors that have a HER2 mutation;

PB272 (neratinib (intravenous)), which we are developing for the treatment of patients with advanced cancer; and

PB357, which we believe can serve as a backup compound to PB272, and which we are evaluating for further development.

We are initially focused on developing neratinib for the treatment of patients with HER2 positive breast cancer, HER2 mutated non-small cell lung cancer, HER2-negative breast cancer that has a HER2 mutation and other solid tumors that have an activating mutation in HER2. Studies show that approximately 20% to 25% of breast cancer tumors have an over-expression of the HER2 protein. Women with breast cancer that over-expresses HER2, referred to as HER2-positive breast cancer, are at greater risk for disease progression and death than women whose tumors do not over-express HER2. Therapeutic strategies, such as the use of Herceptin (trastuzumab), Perjeta (pertuzumab), and Kadcyła (T-DM1), produced by Genentech, and Tykerb (lapatinib), produced by GlaxoSmithKline, given either alone or in combination with chemotherapy, have been developed to improve the treatment of this cancer by binding to the HER2 protein. There are also a number of trials ongoing that involve various combinations of these drugs (for example, Perjeta plus Kadcyła). Based on pre-clinical studies and clinical trials to date, we believe that neratinib may offer an advantage over existing treatments by more potently inhibiting HER2 at a different site and using a different

mechanism than these other drugs.

Currently, the only treatment approved by the U.S. Food and Drug Administration, or FDA, for the treatment of neoadjuvant (newly diagnosed) HER2-positive breast cancer is the combination of Perjeta plus Herceptin and taxane chemotherapy. The FDA-approved therapy for the adjuvant treatment of HER2-positive

S-1

Table of Contents

early stage breast cancer is the combination of Herceptin and taxane chemotherapy. The first-line therapy approved by the FDA for treatment of HER2-positive metastatic breast cancer is the combination of Perjeta plus Herceptin and taxane chemotherapy. The drug Tykerb, given in combination with the chemotherapy drug capecitabine, is also FDA-approved for the treatment of HER2-positive metastatic breast cancer that has failed prior treatment. In a Phase III clinical trial, patients with HER2-positive metastatic breast cancer who received the combination of Tykerb plus capecitabine demonstrated a median progression free survival, or PFS, of 27.1 weeks and a response rate of 23.7%.

In April 2014, we announced the presentation of results from the Phase II clinical trial of neratinib for the neoadjuvant treatment of breast cancer (the I-SPY 2 TRIAL). The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2) is a randomized Phase II clinical trial for women with newly diagnosed Stage 2 or higher (tumor size at least 2.5 cm) breast cancer that addresses whether adding investigational drugs to standard chemotherapy in the neoadjuvant setting is better than standard chemotherapy. The primary endpoint is pathological complete response (pCR) in the breast and the lymph nodes at the time of surgery.

The neratinib-containing regimen (neratinib plus paclitaxel followed by doxorubicin and cyclophosphamide) graduated from the I-SPY 2 TRIAL based on having a high probability of success in Phase III with a signature of HER2-positive/HR-negative. In this group, treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 55.6% compared to the control arm (standard neoadjuvant chemotherapy: paclitaxel in combination with Herceptin (trastuzumab) followed by doxorubicin and cyclophosphamide) which had an estimated pCR rate of 32.6%. The Bayesian probability of superiority for the neratinib-containing regimen (compared to standard therapy) is 94.9%, which is analogous to a p-value of 0.051. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel plus trastuzumab, both followed by doxorubicin/cyclophosphamide, is 79.1%.

For the 65 patients in the trial who were HER2-positive (including those who were either hormone receptor-positive or negative), treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 39.4% compared to the control arm, which demonstrated an estimated pCR rate of 22.8%. The Bayesian probability of superiority for the neratinib-containing regimen is 95.4%, which is analogous to a p-value of 0.046. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel plus trastuzumab is 72.7%.

Patients in the I-SPY 2 TRIAL were screened using the MammaPrint 70-gene signature test to determine if they had a heightened risk of breast cancer recurrence. The median MammaPrint score from the patients in the previous I-SPY 1 TRIAL who fit the eligibility criteria for I-SPY2 was used as a predefined stratification factor for the I-SPY 2 TRIAL. Patients in I-SPY 2 were stratified as either MammaPrint High (below the median from the I-SPY 1 TRIAL) or MammaPrint Ultra High (above the median from I-SPY 1). For the 41 neratinib treated patients in the trial who were MammaPrint Ultra High (80.5% of which were HER2 negative), treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 47.5% compared to the control arm, which demonstrated an estimated pCR rate of 29.4%. The Bayesian probability of superiority for the neratinib-containing regimen is 93.3%, which is analogous to a p-value of 0.067. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel, alone for HER2-negative patients or in combination with trastuzumab for the HER2-positive patients, is 71.8%.

In July 2014, we announced top line results from the Phase III clinical trial of neratinib for the extended adjuvant treatment of breast cancer (the ExteNET Trial). The ExteNET trial is a double-blind, placebo-controlled, Phase III trial of neratinib versus placebo after adjuvant treatment with Herceptin in women with early stage HER2-positive breast cancer. More specifically, the ExteNET trial enrolled 2,821 patients in 41 countries with

S-2

Table of Contents

early-stage HER2-positive breast cancer who had undergone surgery and adjuvant treatment with trastuzumab. After completion of adjuvant treatment with trastuzumab, patients were randomized to receive extended adjuvant treatment with either neratinib or placebo for a period of one year. Patients were then followed for recurrent disease, ductal carcinoma in situ (DCIS), or death for a period of two years after randomization in the trial. The primary endpoint of the trial was disease free survival (DFS). The results of the trial demonstrated that treatment with neratinib resulted in a 33% improvement in disease free survival versus placebo. The hazard ratio was determined to be 0.67, which was statistically significant with a p-value of 0.0046. The secondary endpoint of the trial was disease free survival including ductal carcinoma in situ (DFS-DCIS). The results of the trial demonstrated that treatment with neratinib resulted in a 37% improvement in disease free survival including ductal carcinoma in situ versus placebo. The hazard ratio was determined to be 0.63, which was statistically significant with a p-value of 0.0009. We anticipate presenting and publishing the Phase III trial results in mid-2015 and intend to file for regulatory approval of neratinib in the extended adjuvant setting in the first quarter of 2016. We believe that the worldwide Herceptin adjuvant revenue in 2013 was approximately \$4.3 billion.

In November 2014, we announced top line results from a Phase II clinical trial of neratinib for the treatment of first-line HER2-positive locally recurrent or metastatic breast cancer (the NEfERTT trial). The NEfERTT trial was a randomized, two-arm Phase II trial of neratinib plus the anticancer drug paclitaxel versus trastuzumab (Herceptin) plus paclitaxel as a first-line treatment for HER2-positive locally recurrent or metastatic breast cancer. The trial enrolled 479 patients in 33 countries with locally recurrent or metastatic breast cancer who had not received prior anticancer therapy for locally recurrent or metastatic disease. Patients were randomized to receive first-line treatment with either paclitaxel plus neratinib or paclitaxel plus trastuzumab. The primary endpoint of the trial was PFS. The secondary endpoints of the study included objective response rate and the incidence of central nervous system (CNS) metastases, including brain metastases.

The results of the trial demonstrated that the PFS for the patients who received the combination of paclitaxel plus neratinib was 16.6 months and the PFS for the patients who received the combination of paclitaxel plus trastuzumab was 16.7 months ($p=0.35$). The objective response rate in the trial for the patients who received the combination of paclitaxel plus neratinib was 74.8% and the objective response rate for the patients who received the combination of paclitaxel plus trastuzumab was 75.1% ($p=0.94$). With respect to the incidence of central nervous system metastases (e.g., brain metastases), treatment with the combination of paclitaxel plus neratinib resulted in a 52.6% reduction in the incidence of CNS metastases compared to the incidence of CNS metastases in patients who received the combination of paclitaxel plus trastuzumab. The incidence of CNS metastases was 7.4% in the patients who received paclitaxel plus neratinib, while the incidence of CNS metastases in the patients who received the combination of paclitaxel plus trastuzumab was 15.6% ($p=0.006$). These results reflect a statistically significant difference between the two treatment arms. We believe that this represents the first randomized trial with a HER2 targeted agent that has shown a statistically significant reduction in the incidence of CNS metastases. We anticipate presenting and publishing the Phase II trial results in mid-2015.

Results from a Phase II clinical study, where patients with HER2-positive metastatic breast cancer who had failed prior treatments were administered the combination of neratinib and capecitabine, demonstrated a median PFS of 40.3 weeks and an overall response rate of 64%. In February 2013, we announced that we had reached an agreement with the FDA under a Special Protocol Assessment, or SPA, for our planned Phase III clinical trial of PB272 in patients with HER2-positive metastatic breast cancer who have failed two or more prior treatments (third-line disease). The European Medicines Agency, or EMA, has also provided follow-on scientific advice, or SA, consistent with that of the FDA regarding our Phase III trial design and endpoints to be used and ability of such design to support the submission of a European Union, or EU, Market Authorization Application, or MAA. We commenced our Phase III clinical trial of neratinib (oral) for breast cancer patients who have previously failed two or more prior HER2-directed treatments in the second quarter of 2013.

S-3

Table of Contents

We are also exploring the safety and efficacy of neratinib (oral):

in combination with temsirolimus in patients with HER 2-positive metastatic breast cancer who have failed multiple prior treatments;

for the treatment of patients with HER2-positive metastatic breast cancer with brain metastases;

for the treatment of HER2-positive neoadjuvant breast cancer;

for the extended adjuvant treatment of HER2-positive breast cancer in patients who have completed adjuvant treatment with Herceptin;

for the treatment of patients with first line HER2-positive metastatic breast cancer who have not previously received treatment in the metastatic setting;

for the treatment of HER2 mutated non-small cell lung cancer;

for the treatment of patients with HER2-negative breast cancer that has a HER2 mutation; and

for the treatment of patients with solid tumors who have an activating HER2 mutation.

We have ongoing clinical trials for each of these indications and expect to report results from certain of these clinical trials in 2015.

We licensed the exclusive worldwide rights to our current drug candidates from Pfizer Inc., or Pfizer, which had previously been responsible for the clinical trials regarding neratinib. We have modified Pfizer's original clinical development strategy and during the next 12 to 18 months we plan to:

continue our Phase III clinical trials of neratinib in patients with HER2-positive metastatic breast cancer who have previously failed two or more prior treatments;

commence a Phase III trial of neratinib for the neoadjuvant treatment of HER2-positive breast cancer and for the neoadjuvant treatment of a subset of patients with HER2-negative breast cancer;

continue the ongoing Phase II clinical trials of neratinib in the neoadjuvant treatment of HER2-positive breast cancer, the ongoing Phase II trial in patients with HER2-positive metastatic breast cancer that has

metastasized to the brain, the ongoing Phase II trial in the treatment of HER2 mutated non-small cell lung cancer, the ongoing Phase II trial in the treatment of patients with HER2-negative breast cancer that have a HER2 mutation, the ongoing Phase II trial in the treatment of solid tumors that have an activating HER2 mutation, the ongoing Phase III trial for the extended adjuvant treatment of HER2 positive breast cancer in patients who have completed adjuvant treatment with Herceptin, and the ongoing Phase II trial for the treatment of patients with first line HER2-positive metastatic breast cancer who have not previously received treatment in the metastatic setting; and

continue to evaluate the application of neratinib in the treatment of other forms of HER2-positive or HER2 mutated cancers where there may be unmet medical needs.

Risks Affecting Us

Our business is subject to numerous risks, as more fully described in the section of this prospectus entitled Risk Factors, including the following:

We currently have no product revenues and no products approved for marketing, and will need to raise additional capital to operate our business.

Table of Contents

We have a limited operating history and are not profitable and may never become profitable.

We are heavily dependent on the success of neratinib (oral), our lead drug candidate, which is still under clinical development, and we cannot be certain that neratinib (oral) will receive regulatory approval or be successfully commercialized even if we receive regulatory approval.

Clinical trials are very expensive, time-consuming and difficult to design and implement.

The results of our clinical trials may not support our drug candidate claims.

We depend significantly on intellectual property licensed from Pfizer and the termination of this license would significantly harm our business and future prospects.

Our ability to commercialize our potential products will depend on our ability to sell such products without infringing the patent or proprietary rights of third parties. If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any such litigation would have a material adverse effect on our business.

Corporate Information

Our principal executive offices are located at 10880 Wilshire Boulevard, Suite 2150, Los Angeles, California 90024. Our telephone number is (424) 248-6500. Our website is www.pumabiotechnology.com. Information contained on our website is not incorporated by reference into, and should not be considered a part of, this prospectus supplement.

Table of Contents

THE OFFERING

Common Stock Offered by Us	1,000,000 shares
Common Stock Outstanding After this Offering	31,117,819 shares (or 31,267,819 shares if the underwriters exercise their option to purchase additional shares in full)
Option to Purchase Additional Shares	The underwriters have a 30-day option to purchase up to an additional 150,000 shares of our common stock at the public offering price less the underwriting discounts and commissions.
Use of Proceeds	We intend to use the net proceeds of this offering for the overall development of our drug candidates, including, but not limited to, research and development and clinical trial expenditures, and for general corporate and working capital purposes. See Use of Proceeds.
Risk Factors	You should read the Risk Factors section beginning on page S-7 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement, for a discussion of factors to consider before deciding to invest in shares of our common stock.

New York Stock Exchange Symbol **PBYI**

Unless otherwise noted, the number of shares of our common stock outstanding prior to and after this offering is based on 30,117,819 shares outstanding as of September 30, 2014, and excludes:

3,778,307 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2014 at a weighted average exercise price of \$55.12 per share;

a maximum of 28,411 shares of common stock issuable pursuant to performance share awards outstanding as of September 30, 2014;

2,396,405 shares of common stock reserved for future issuance under our incentive award plan; and

2,116,250 shares of our common stock issuable upon the exercise of a warrant held by Alan H. Auerbach, our President and Chief Executive Officer, at \$16.00 per share.

Unless otherwise indicated, the information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares of common stock from us.

S-6

Table of Contents

RISK FACTORS

*Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should carefully consider the risks discussed below, together with the other information contained in this prospectus supplement, the accompanying prospectus or incorporated by reference herein or therein, including the risks and uncertainties discussed under **Risk Factors** in our Annual Report on Form 10-K for the fiscal year ended December 31, 2013, which are incorporated by reference into this prospectus supplement. If any of the risks incorporated by reference or set forth below occurs, our business, results of operations and financial condition could suffer significantly. As a result, you could lose some or all of your investment in our common stock. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business.*

Risks Related to this Offering

Our stock price may fluctuate significantly and you may have difficulty selling your shares based on current trading volumes of our stock. In addition, numerous other factors could result in substantial volatility in the trading price of our stock.

Our common stock has been listed on the New York Stock Exchange since October 19, 2012. Prior to October 2012, shares of our common stock had been quoted for trading on the OTC Bulletin Board and OTCQB Market in limited volumes. We cannot predict the extent to which investor interest in our company will be sufficient to maintain an active trading market on the New York Stock Exchange or any other exchange in the future. We have several stockholders, including affiliated stockholders, who hold substantial blocks of our stock. As of December 31, 2014, we had 30,548,309 shares of common stock outstanding, and stockholders holding at least 5% of our stock, individually or with affiliated entities, collectively beneficially owned or controlled approximately 58.6% of such shares. Sales of large numbers of shares by any of our large stockholders could adversely affect our trading price, particularly given our relatively small historic trading volumes. If stockholders holding shares of our common stock sell, indicate an intention to sell, or if it is perceived that they will sell, substantial amounts of their common stock in the public market, the trading price of our common stock could decline. Moreover, if there is no active trading market or if the volume of trading is limited, holders of our common stock may have difficulty selling their shares.

The price of our common stock could be subject to volatility related or unrelated to our operations.

The trading price of our common stock may be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. These factors include:

actual or anticipated quarterly variation in our results of operations or the results of our competitors;

announcements of medical innovations or new products by our competitors;

announcements regarding results of any clinical trials relating to our drug candidates;

issuance of new or changed securities analysts' reports or recommendations for our stock;

developments or disputes concerning our intellectual property or other proprietary rights;

commencement of, or involvement in, litigation;

market conditions in the biopharmaceutical industry;

timing and announcement of regulatory approvals;

S-7

Table of Contents

any future sales of our common stock or other securities in connection with raising additional capital or otherwise;

any major change to the composition of our board of directors or management; and

general economic conditions and slow or negative growth of our markets.

The stock market in general, and market prices for the securities of technology-based companies like ours in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common stock, regardless of our operating performance. In several recent situations where the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.

Investors in this offering will suffer immediate and substantial dilution in the book value of their investment.

If you purchase common stock in this offering, you will pay more for your shares than our net tangible book value per share. Based upon an assumed public offering price of \$215.52 per share, the last reported sale price of our common stock on the New York Stock Exchange on January 16, 2015, you will incur immediate and substantial dilution of \$204.47 per share, representing the difference between our public offering price and our net tangible book value per share as of September 30, 2014. Furthermore, if the underwriters exercise their option to purchase additional shares of our common stock, you could experience further dilution. You will experience additional dilution upon exercise of any warrant, upon exercise of options to purchase shares of common stock under our incentive award plan, or if we otherwise issue additional shares of our common stock. For a further description of the dilution that you will experience immediately after this offering, see Dilution.

A substantial number of shares of common stock may be sold in the market following this offering, which may depress the market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market following this offering could cause the market price of our common stock to decline. A substantial majority of the outstanding shares of our common stock are, and the shares of common stock sold in this offering upon issuance will be, freely tradable without restriction or further registration under the Securities Act of 1933, as amended.

Our management will have broad discretion over the use of the proceeds we receive in this offering and might not apply the proceeds in ways that increase the value of your investment.

Our management will have broad discretion to use the net proceeds from this offering, and you will be relying on the judgment of our management regarding the application of these proceeds. Our management might not apply the net proceeds of this offering in ways that increase the value of your investment.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, and the SEC filings that are incorporated by reference into this prospectus supplement and the accompanying prospectus contain or incorporate by reference forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, which we refer to as the Securities Act, and Section 21E of the Securities Exchange Act of 1934, which we refer to as the Exchange Act. These statements are often, but not always, made through the use of words or phrases such as anticipate, estimate, plan, project, continuing, ongoing, expect, believe, intend and similar words or phrases. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Accordingly, these statements involve estimates, assumptions, risks and uncertainties, including the risks discussed in the section entitled Risk Factors, that could cause actual results to differ materially from those expressed in them. You should not place undue reliance on these forward-looking statements. Although forward-looking statements reflect management's good faith beliefs, reliance should not be placed on forward-looking statements because they involve known and unknown risks, uncertainties and other factors, which may cause the actual results, performance or achievements to differ materially from anticipated future results, performance or achievements expressed or implied by such forward-looking statements. These forward-looking statements include, but are not limited to, statements about:

the development of our drug candidates, including when we expect to undertake, initiate and complete clinical trials of our product candidates;

the regulatory approval of our drug candidates;

our use of clinical research organizations and other contractors;

our ability to find collaborative partners for research, development and commercialization of potential products;

our ability to market any of our products;

our history of operating losses;

our expectations regarding our costs and expenses;

our anticipated capital requirements and estimates regarding our needs for additional financing;

our ability to compete against other companies and research institutions;

our ability to secure adequate protection for our intellectual property;

our ability to attract and retain key personnel; and

our ability to obtain adequate financing.

Discussions containing these forward-looking statements may be found throughout this prospectus supplement, the accompanying prospectus, and the SEC filings that are incorporated by reference into this prospectus supplement and the accompanying prospectus. Forward-looking statements speak only as of the date the statements are made. We undertake no obligation to update the forward-looking statements or to reflect events or circumstances. The risks discussed in this prospectus supplement, the accompanying prospectus, and the SEC filings that are incorporated by reference into this prospectus supplement and the accompanying prospectus should be considered in evaluating our prospects and future financial performance.

S-9

Table of Contents

USE OF PROCEEDS

At the assumed public offering price of \$215.52 per share, the last reported sale price of our common stock on the New York Stock Exchange on January 16, 2015, we estimate that the net proceeds from this offering will be approximately \$202.2 million (or \$232.6 million if the underwriters exercise their option to purchase additional shares in full), after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Each \$10.00 increase (decrease) in the assumed public offering price of \$215.52 would increase (decrease) the net proceeds to us from this offering by approximately \$9.4 million, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, assuming that the number of shares offered by us, as set forth above, remains the same. Each increase (decrease) of 100,000 shares in the number of shares offered by us at the assumed public offering price would increase (decrease) the net proceeds to us in this offering by approximately \$20.3 million. We do not expect that a change in the public offering price or the number of shares by these amounts would have a material effect on our uses of the proceeds from this offering, although it may impact the amount of time prior to which we will need to seek additional capital.

We intend to use the net proceeds to us from this offering for the overall development of our drug candidates, including, but not limited to, research and development and clinical trial expenditures, and for general corporate and working capital purposes. Pending the application of the net proceeds as described above, we intend to invest the net proceeds of the offering in short-term, investment-grade, interest-bearing securities. We currently intend to file a new drug application, or NDA, for the approval of neratinib in the extended adjuvant setting in the first quarter of 2016. Assuming we file the NDA as intended, we expect that our existing cash and cash equivalents, together with the net proceeds from this offering, will be sufficient to fund our operations through the anticipated approval of the NDA.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds to us from this offering and investors will be relying on the judgment of our management regarding the application of the proceeds from this offering. We reserve the right to change the use of these proceeds as a result of certain contingencies such as competitive developments, the results of our commercialization efforts, acquisition and investment opportunities and other factors.

Table of Contents**PRICE RANGE OF COMMON STOCK**

From April 20, 2012 through October 18, 2012, shares of our common stock were quoted on the OTC Bulletin Board, or OTCBB*, under the symbol PBYI. On October 19, 2012, shares of our common stock commenced trading on the New York Stock Exchange, or NYSE, under the symbol PBYI and ceased being quoted on the OTCBB. The high and low bid quotations of our common stock on the OTCBB and the high and low sales prices of our common stock on the NYSE are set forth below:

Fiscal Year 2012	High	Low
First Quarter	\$	\$
Second Quarter	14.03	10.00
Third Quarter	15.00	11.00
Fourth Quarter	23.25	15.00
OTCBB: October 1 18	17.25	15.00
NYSE: October 19 December 31	23.25	15.45
Fiscal Year 2013		
First Quarter	34.98	18.47
Second Quarter	45.69	27.40
Third Quarter	62.66	44.39
Fourth Quarter	112.46	33.70
Fiscal Year 2014		
First Quarter	143.65	97.31
Second Quarter	118.22	53.63
Third Quarter	279.37	57.25
Fourth Quarter	255.43	181.60
Fiscal Year 2015		
First Quarter (through January 16, 2015)	215.88	185.83

* The OTCBB is a quotation medium for subscribing members, not an issuer listing service. OTCBB securities are traded by a community of market makers that enter quotes and trade reports through a closed computer network. The last reported sale price for our common stock on January 16, 2015 was \$215.52 per share. On January 13, 2015, we had 29 holders of record of our common stock. We believe approximately 10,910 additional owners held our common stock in street name as of that date.

DIVIDEND POLICY

We never have declared or paid any cash dividends on our capital stock. Currently, we anticipate that we will retain all available funds for use in the operation and expansion of our business and do not anticipate paying any cash dividends after the offering and for the foreseeable future. Any future determination relating to dividend policy will be made at the discretion of our board of directors and will depend on our future earnings, capital requirements, financial condition, prospects, applicable Delaware law, which provides that dividends are only payable out of surplus or current net profits, and other factors that our board of directors deems relevant.

S-11

Table of Contents**DILUTION**

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock upon closing of this offering. Net tangible book value per share of our common stock is determined at any date by subtracting our total liabilities from the amount of our total tangible assets (total assets less intangible assets) and dividing the difference by the number of shares of our common stock deemed to be outstanding at that date.

Our net tangible book value as of September 30, 2014 was approximately \$141.6 million, or \$4.70 per share, based on 30,117,819 shares of common stock outstanding as of September 30, 2014. After giving effect to our sale of 1,000,000 shares of common stock in this offering at an assumed public offering price of \$215.52 per share, the last reported sale price of our common stock on the New York Stock Exchange on January 16, 2015, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2014 would have been \$343.8 million, or \$11.05 per share. This amount represents an immediate increase in net tangible book value of \$6.35 per share of our common stock to existing stockholders and an immediate dilution in net tangible book value of \$204.47 per share of our common stock to new investors purchasing shares of common stock in this offering.

The following tables illustrate this dilution on a per share basis:

Assumed public offering price per share	\$ 215.52
Net tangible book value per share as of September 30, 2014 before giving effect to this offering	\$ 4.70
Increase in net tangible book value per share attributable to this offering	\$ 6.35
As adjusted net tangible book value per share after this offering	\$ 11.05
Dilution per share to new investors in this offering	\$ 204.47

Each \$10.00 increase (decrease) in the assumed public offering price of \$215.52 per share would increase (decrease) the as adjusted net tangible book value per share after this offering by approximately \$0.30 and dilution per share to new investors by approximately \$9.70, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We may also increase or decrease the number of shares we are offering. Each increase of 100,000 shares in the number of shares offered by us would increase our as adjusted net tangible book value per share after this offering by approximately \$0.61 per share and decrease the dilution to new investors by approximately \$0.61 per share, assuming that the public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Each decrease of 100,000 shares in the number of shares offered by us would decrease our as adjusted net tangible book value per share after this offering by approximately \$0.62 per share and increase the dilution to new investors by approximately \$0.62 per share, assuming that the public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated offering

expenses payable by us.

The information above assumes that the underwriters do not exercise their option to purchase additional shares. If the underwriters exercise their option to purchase additional shares of our common stock in full, the as adjusted net tangible book value per share after giving effect to this offering would be \$11.97 per share, which amount represents an immediate increase in as adjusted net tangible book value of \$7.27 per share of our common stock to existing stockholders and an immediate dilution per share to new investors in this offering of \$203.55 per share.

S-12

Table of Contents

The discussion and table above exclude, as of September 30, 2014:

3,778,307 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2014 at a weighted average exercise price of \$55.12 per share;

a maximum of 28,411 shares of common stock issuable pursuant to performance share awards outstanding as of September 30, 2014;

2,396,405 shares of common stock reserved for future issuance under our incentive award plan; and

2,116,250 shares of our common stock issuable upon the exercise of a warrant held by Alan H. Auerbach, our President and Chief Executive Officer, at \$16.00 per share.

To the extent that any of these shares are issued upon exercise of stock options or warrants, there may be further dilution to new public investors. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital by issuing equity securities or convertible debt, your ownership will be further diluted.

Table of Contents

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or non-U.S. tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended (the Code), Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service (the IRS), in each case in effect as of the date hereof. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder of our common stock. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to that discussed below regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder's particular circumstances, including the impact of the Medicare contribution tax on net investment income. In addition, it does not address consequences relevant to Non-U.S. Holders subject to special rules, including, without limitation:

U.S. expatriates and certain former citizens or long-term residents of the United States;

persons subject to the alternative minimum tax;

persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;

banks, insurance companies, and other financial institutions;

real estate investment trusts or regulated investment companies;

brokers, dealers or traders in securities or currencies;

controlled foreign corporations, passive foreign investment companies, and corporations that accumulate earnings to avoid U.S. federal income tax;

S corporations, partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);

tax-exempt organizations or governmental organizations;

persons deemed to sell our common stock under the constructive sale provisions of the Code;

persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and

tax-qualified retirement plans.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships

S-14

Table of Contents

holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATION PURPOSES ONLY AND IS NOT, AND IS NOT INTENDED AS, LEGAL OR TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a Non-U.S. Holder is any beneficial owner of our common stock that is neither a U.S. person nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

an individual who is a citizen or resident of the United States;

a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes) created or organized under the laws of the United States, any state thereof, or the District of Columbia;

an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more United States persons (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

As described in the section entitled Dividend Policy, we do not anticipate declaring or paying dividends to holders of our common stock in the foreseeable future. However, if we do make distributions of cash or property on our common stock, such distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder's adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under Sale or Other Taxable Disposition.

Subject to the discussion below on effectively connected income, dividends paid to a Non-U.S. Holder of our common stock will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty, provided the Non-U.S. Holder furnishes a valid IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) certifying qualification for the lower treaty rate). A Non-U.S. Holder that does not timely furnish the required documentation, but that qualifies for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), the Non-U.S. Holder will be exempt from the U.S. federal withholding tax described above. To claim the exemption,

S-15

Table of Contents

the Non-U.S. Holder must furnish to the applicable withholding agent a valid IRS Form W-8ECI, certifying that the dividends are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States.

Any such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular graduated rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Sale or Other Taxable Disposition

A Non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);

the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or

our common stock constitutes a U.S. real property interest ("USRPI") by reason of our status as a U.S. real property holding corporation ("USRPHC") for U.S. federal income tax purposes.

Gain described in the first bullet point above generally will be subject to U.S. federal income tax on a net income basis at the regular graduated rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

Gain described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty), which may be offset by U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States), provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we currently are not, and do not anticipate becoming, a USRPHC. Because the determination of whether we are a USRPHC depends, however, on the fair market value of our USRPIs relative to the fair market value of our non-U.S. real property interests and our other business assets, there can be no assurance we currently are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition by a Non-U.S. Holder of our common stock will not be subject to U.S. federal income tax if our common stock is regularly traded, as defined by applicable Treasury Regulations, on an established securities market, and such Non-U.S. Holder owned, actually or constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the Non-U.S. Holder's holding period.

Non-U.S. Holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Payments of dividends on our common stock will not be subject to backup withholding, provided the applicable withholding agent does not have actual knowledge or reason to know the holder is a United States

S-16

Table of Contents

person and the holder either certifies its non-U.S. status, such as by furnishing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or otherwise establishes an exemption. However, information returns are required to be filed with the IRS in connection with any dividends on our common stock paid to the Non-U.S. Holder, regardless of whether any tax was actually withheld. In addition, proceeds of the sale or other taxable disposition of our common stock within the United States or conducted through certain U.S.-related brokers generally will not be subject to backup withholding or information reporting, if the applicable withholding agent receives the certification described above and does not have actual knowledge or reason to know that such holder is a United States person, or the holder otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Copies of information returns that are filed with the IRS may also be made available under the provisions of an applicable treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under Sections 1471 to 1474 of the Code (such Sections commonly referred to as the Foreign Account Tax Compliance Act, or "FATCA") on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution or a non-financial foreign entity (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any substantial United States owners (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain specified United States persons or United States-owned foreign entities (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations, withholding under FATCA generally applies to payments of dividends on our common stock made on or after July 1, 2014 and will apply to payments of gross proceeds from the sale or other disposition of such stock on or after January 1, 2017.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

Table of Contents**UNDERWRITING**

Merrill Lynch, Pierce, Fenner & Smith Incorporated and J.P. Morgan Securities LLC are acting as lead book-running managers and representatives of each of the underwriters named below. Citigroup Global Markets Inc. is acting as joint book-running manager. Subject to the terms and conditions set forth in an underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
J.P. Morgan Securities LLC	
Citigroup Global Markets Inc.	
Leerink Partners LLC	
Cowen and Company, LLC	
 Total	 1,000,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of these shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officer's certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus supplement and to dealers at that price less a concession not in excess of \$ _____ per share. After the initial offering, the public offering price, concession or any other term of the offering may be changed. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The following table shows the public offering price, underwriting discount and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares.

	Per Share	Without Option	With Option
Public offering price	\$	\$	\$
Underwriting discount	\$	\$	\$
Proceeds, before expenses, to us	\$	\$	\$

The expenses of the offering, not including the underwriting discount, are estimated at \$375,000 and are payable by us. We have also agreed to reimburse the underwriters for certain expenses.

S-18

Table of Contents

Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus supplement, to purchase up to 150,000 additional shares at the public offering price, less the underwriting discount. If the underwriters exercise this option, each will be obligated, subject to conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We and our executive officers and directors have agreed not to sell or transfer any common stock or securities convertible into, exchangeable for, exercisable for, or repayable with common stock, for 90 days after the date of this prospectus supplement without first obtaining the written consent of the representatives. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

offer, pledge, sell or contract to sell any common stock,

sell any option or contract to purchase any common stock,

purchase any option or contract to sell any common stock,

grant any option, right or warrant for the sale of any common stock,

lend or otherwise dispose of or transfer any common stock,

request or demand that we file a registration statement related to the common stock, or

enter into any swap or other agreement that transfers, in whole or in part, the economic consequence of ownership of any common stock whether any such swap or transaction is to be settled by delivery of shares or other securities, in cash or otherwise.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for or repayable with common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition.

New York Stock Exchange Listing

The shares are listed on the New York Stock Exchange under the symbol **PBYI**.

Price Stabilization, Short Positions

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representatives may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with the offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. Covered short sales are sales made in an amount not greater than the underwriters option to purchase additional shares described above. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares

Table of Contents

in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option granted to them. Naked short sales are sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the completion of the offering.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriters may conduct these transactions on the New York Stock Exchange, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

In connection with the offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

Some of the underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates. They have received, or may in the future receive, customary fees and commissions for these transactions.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of shares may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

- B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or

- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

S-20

Table of Contents

provided that no such offer of shares shall require us or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

The Company, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the Company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression an offer to the public in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression Prospectus Directive means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are qualified investors (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). This document must not be acted on or relied on in the United Kingdom by persons who are not relevant persons. In the United Kingdom, any investment or investment activity to which this document relates is only available to, and will be engaged in with, relevant persons.

Notice to Prospective Investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has

S-21

Table of Contents

been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

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

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus supplement is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for the prospectus supplement. The shares to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus supplement you should consult an authorized financial advisor.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission (ASIC), in relation to the offering. This prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001 (the Corporations Act), and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons (the Exempt Investors) who are sophisticated investors (within the meaning of section 708(8) of the Corporations Act), professional investors (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this

prospectus is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

S-22

Table of Contents

Notice to Prospective Investors in Hong Kong

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

Notice to Prospective Investors in Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph,

Japanese Person shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

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

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

(a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

S-23

Table of Contents

- (b) where no consideration is or will be given for the transfer;
- (c) where the transfer is by operation of law;
- (d) as specified in Section 276(7) of the SFA; or
- (e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

S-24

Table of Contents

LEGAL MATTERS

Legal matters in connection with the validity of the shares offered by this prospectus supplement will be passed upon by Latham & Watkins LLP, Costa Mesa, California. Certain legal matters in connection with this offering will be passed upon for the underwriters by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts.

EXPERTS

The consolidated financial statements incorporated by reference into this prospectus supplement from Puma Biotechnology, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2013, including schedules appearing therein, and the effectiveness of Puma Biotechnology Inc.'s internal control over financial reporting as of December 31, 2013, have been audited by PKF Certified Public Accountants, A Professional Corporation, independent registered public accounting firm, as set forth in their reports thereon incorporated by reference therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein in reliance upon the reports of PKF Certified Public Accountants, A Professional Corporation, pertaining to such consolidated financial statements and the effectiveness of our internal control over financial reporting given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is <http://www.sec.gov>.

Our web site address is www.pumabiotechnology.com. The information on our web site, however, is not, and should not be deemed to be, a part of this prospectus supplement.

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to incorporate by reference information into this prospectus supplement and the accompanying prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement and the accompanying prospectus, and subsequent information that we file with the SEC will

automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement and the accompanying prospectus to the extent that a statement contained in this prospectus supplement and the accompanying prospectus modifies or replaces that statement.

S-25

Table of Contents

We incorporate by reference the following information or documents that we have filed with the SEC:

Our Annual Report on Form 10-K for the year ended December 31, 2013, filed with the SEC on March 3, 2014.

Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2014, June 30, 2014 and September 30, 2014, filed with the SEC on May 12, 2014, August 11, 2014 and November 10, 2014, respectively.

Our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 30, 2014, as amended on June 4, 2014.

Our Current Reports on Form 8-K filed with the SEC on February 6, 2014, April 7, 2014 (including Exhibit 99.1), May 14, 2014, May 23, 2014, June 2, 2014, June 11, 2014, July 22, 2014, September 3, 2014, September 29, 2014, November 13, 2014, November 20, 2014, December 3, 2014 and December 12, 2014.

The description of our Common Stock contained in our Registration Statement on Form 8-A, dated and filed with the SEC on October 16, 2012, and any amendment or report filed with the SEC for the purpose of updating the description.

We incorporate by reference into this prospectus supplement and accompanying prospectus all reports and other documents we subsequently file with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, between the date of this prospectus supplement and the termination of the offering of the securities described in this prospectus supplement. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed above or filed in the future, that are not deemed filed with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K. The reports and documents specifically listed above or filed in the future (excluding any information furnished to, rather than filed with, the SEC) are deemed to be part of this prospectus supplement and accompanying prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference into this prospectus supplement (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Puma Biotechnology, Inc.
10880 Wilshire Boulevard, Suite 2150
Los Angeles, California 90024
Attention: Investor Relations

Telephone: (424) 248-6500

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement and the accompanying prospectus.

S-26

Table of Contents

PROSPECTUS

PUMA BIOTECHNOLOGY, INC.

Common Stock

Debt Securities

Warrants

Units

We may offer and sell the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled *About this Prospectus* and *Plan of Distribution* for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE RISK FACTORS ON PAGE 5 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on the New York Stock Exchange under the symbol *PBYI*. On January 16, 2015, the last reported sale price of our common stock on the New York Stock Exchange was \$215.52 per share.

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 January 20, 2015.

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE</u>	2
<u>THE COMPANY</u>	4
<u>RISK FACTORS</u>	5
<u>USE OF PROCEEDS</u>	6
<u>RATIO OF EARNINGS TO FIXED CHARGES</u>	7
<u>DESCRIPTION OF CAPITAL STOCK</u>	8
<u>DESCRIPTION OF DEBT SECURITIES</u>	11
<u>DESCRIPTION OF OTHER SECURITIES</u>	19
<u>GLOBAL SECURITIES</u>	20
<u>PLAN OF DISTRIBUTION</u>	23
<u>LEGAL MATTERS</u>	24
<u>EXPERTS</u>	24

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission, or the SEC, as a well-known seasoned issuer as defined in Rule 405 under the Securities Act of 1933, as amended, using a shelf registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you should rely on the prospectus supplement or any related free writing prospectus. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement, together with the additional information described under the heading **Where You Can Find More Information; Incorporation by Reference**.

We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate as of the date on its respective cover, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates.

When we refer to **Puma**, **we**, **our**, **us** and the **Company** in this prospectus, we mean Puma Biotechnology, Inc. and its wholly-owned subsidiary, Puma Biotechnology Ltd, unless otherwise specified. When we refer to **you**, we mean the investors in the applicable series of securities.

Table of Contents

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is <http://www.sec.gov>.

Our web site address is www.pumabiotechnology.com. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our securities.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to incorporate by reference information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus modifies or replaces that statement.

We incorporate by reference our documents listed below (File No. 001-35703) and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act in this prospectus, between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed filed with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC:

Edgar Filing: PUMA BIOTECHNOLOGY, INC. - Form 424B5

Our Annual Report on Form 10-K for the year ended December 31, 2013, filed with the SEC on March 3, 2014.

Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2014, June 30, 2014 and September 30, 2014, filed with the SEC on May 12, 2014, August 11, 2014 and November 10, 2014, respectively.

Table of Contents

Our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 30, 2014, as amended on June 4, 2014.

Our Current Reports on Form 8-K filed with the SEC on February 6, 2014, April 7, 2014 (including Exhibit 99.1), May 14, 2014, May 23, 2014, June 2, 2014, June 11, 2014, July 22, 2014, September 3, 2014, September 29, 2014, November 13, 2014, November 20, 2014, December 3, 2014 and December 12, 2014.

The description of our Common Stock contained in our Registration Statement on Form 8-A, dated and filed with the SEC on October 16, 2012, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Puma Biotechnology, Inc.
10880 Wilshire Boulevard, Suite 2150
Los Angeles, California 90024
Attention: Investor Relations
Telephone: (424) 248-6500

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus and any accompanying prospectus supplement.

Table of Contents

THE COMPANY

Puma Biotechnology, Inc. is a development stage biopharmaceutical company that acquires and develops innovative products for the treatment of various forms of cancer. We focus on in-licensing drug candidates that are undergoing or have already completed initial clinical testing for the treatment of cancer and then seek to further develop those drug candidates for commercial use. We are initially focused on the development of PB272 (oral neratinib), a potent irreversible tyrosine kinase inhibitor, for the treatment of patients with HER2-positive breast cancer and patients with non-small cell lung cancer, breast cancer and other solid tumors that have a HER2 mutation.

We were incorporated on April 27, 2007 in the State of Delaware under the name Innovative Acquisitions Corp. Until October 4, 2011, we were a shell company with nominal assets and no operations. On September 29, 2011, we entered into an Agreement and Plan of Merger with IAC Merger Corporation, a Delaware corporation and our wholly-owned subsidiary, or Merger Sub, and Puma Biotechnology, Inc., a private Delaware corporation, or Former Puma. On October 4, 2011, Merger Sub merged with and into Former Puma, and Former Puma, as the surviving entity, became our wholly-owned subsidiary. Upon completion of the merger, Former Puma, our wholly-owned subsidiary, merged with and into us, leaving us as the surviving corporation. We adopted Former Puma's business plan and changed our name to Puma Biotechnology, Inc. In November 2012, we established and incorporated Puma Biotechnology Ltd, a wholly-owned subsidiary, for the sole purpose of serving as our legal representative in the United Kingdom and the European Union in connection with our clinical trial activity in those countries.

Our principal executive offices are located at 10880 Wilshire Boulevard, Suite 2150, Los Angeles, California 90024, and our telephone number is (424) 248-6500.

Table of Contents

RISK FACTORS

Investment in any securities offered pursuant to this prospectus and the applicable prospectus supplement involves risks. You should carefully consider the risk factors in our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q or Current Reports on Form 8-K we file after the date of this prospectus, which are incorporated by reference herein, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement before acquiring any of such securities. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Table of Contents

USE OF PROCEEDS

We intend to use the net proceeds from the sale of the securities as set forth in the applicable prospectus supplement.

Table of Contents**RATIO OF EARNINGS TO FIXED CHARGES**

The following table sets forth the historical ratios of earnings to fixed charges for us and our consolidated subsidiary for the periods indicated.

	Year Ended December 31,				Nine Months
	2010 (x)	2011	2012	2013	Ended September 30, 2014
Ratio of earnings to fixed charges	N/A	N/A	N/A	N/A	N/A

(x) From inception (September 15, 2010) through December 31, 2010.

For purposes of calculating the ratio of earnings to fixed charges, earnings (loss) consist of income (loss) before income taxes plus fixed charges. Fixed charges include interest expense, non-cash interest expense and other, and an estimate of the interest expense within rental expense.

We incurred net losses of approximately \$0.007 million, \$10.2 million, \$74.4 million, \$54.7 million and \$94.5 million for the years ended December 31, 2010, 2011, 2012, 2013 and the nine months ended September 30, 2014, respectively, and did not have any fixed charges for such periods. Accordingly, we are unable to disclose a ratio of earnings to fixed charges for such periods.

Table of Contents

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is only a summary, and is qualified in its entirety by reference to the actual terms and provisions of the capital stock contained in our certificate of incorporation, our bylaws, and other agreements to which we and our stockholders are parties, which has been publicly filed with the SEC. See [Where You Can Find More Information](#); [Incorporation by Reference](#).

General

We currently have authorized capital stock of 100,000,000 shares, which are designated as common stock, par value \$0.0001 per share. As of January 13, 2015, we had 30,644,420 shares of common stock outstanding held of record by 29 stockholders. Since many stockholders hold shares in [street name](#), we believe that the number of beneficial owners of shares of our common stock was significantly larger than the number of record holders. In addition, as of January 13, 2015, there were outstanding options to purchase 3,691,460 shares of common stock.

The holders of our common stock are entitled to one vote per share on matters on which our stockholders vote. There are no cumulative voting rights. Holders of our common stock are entitled to receive dividends, if declared by our board of directors, out of funds that we may legally use to pay dividends. If we liquidate or dissolve, holders of our common stock are entitled to share ratably in our assets once our debts are paid. Our amended and restated certificate of incorporation does not provide our common stock with any redemption, conversion or preemptive rights.

Dividend Policy

In the past, we have not distributed earnings to stockholders. Any future decisions regarding dividends will be made by our board of directors. We currently intend to retain and use any future earnings for the development and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Our board of directors has complete discretion on whether to pay dividends. Even if our board of directors decides to pay dividends, the form, frequency and amount will depend upon our future operations and earnings, capital requirements and surplus, general financial condition, contractual restrictions and other factors that the board may deem relevant.

Registration Rights

Pursuant to the terms of a registration rights agreement, as amended, between us and certain of our stockholders, we maintain an effective registration statement registering the resale of shares of our common stock by certain of our stockholders. As of April 2013, the most recent effective date of the registration statement, approximately 10,942,158 shares of our common stock remained available for resale under the registration statement. The registration rights agreement, as amended, also gives investors certain co-sale rights with respect to a firm commitment underwritten offering of the shares of our common stock held by Alan H. Auerbach, our President and Chief Executive Officer.

Warrant

In October 2011, Alan H. Auerbach, our Chairman, Chief Executive Officer and President was issued a warrant that entitled him to maintain ownership of at least 20% of our common stock following our public offering that closed in October 2012. The warrant entitles Mr. Auerbach to acquire 2,116,250 shares of our common stock at \$16 per share. The warrant is exercisable until October 2021.

Indemnification of Directors and Officers

Section 145 of the Delaware General Corporation Law authorizes a corporation to grant, and authorizes a court to award, indemnity to officers, directors and other corporate agents. As permitted by Section 102(b)(7) of

Table of Contents

the Delaware General Corporation Law, our certificate of incorporation includes a provision that eliminates the personal liability of our directors for breach of their fiduciary duty as directors, except that a director shall be liable to the extent provided by applicable law (i) for breach of the director's duty of loyalty to us or our stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) pursuant to Section 174 of the Delaware General Corporation Law or (iv) for any transaction from which the director derived an improper personal benefit. These indemnification provisions may be sufficiently broad to permit indemnification of our officers and directors for liabilities (including reimbursement of expenses incurred) arising under the Securities Act of 1933, as amended, or the Securities Act.

To the extent that indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or persons controlling our Company pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable. If a claim for indemnification against such liabilities (other than the payment by us of expenses incurred or paid by a director, officer or controlling person of our company in the successful defense of any action, suit or proceeding) is asserted by any of our directors, officers or controlling persons in connection with the securities being registered, we will, unless in the opinion of our counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by us is against public policy as expressed in the Securities Act and will be governed by the final adjudication of that issue.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the Delaware General Corporation Law. This statute regulating corporate takeovers prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for three years following the date that the stockholder became an interested stockholder, unless:

prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

upon completion of the transaction that resulted in the interested stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers, and (b) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to the date of the transaction, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is any person who, together with such person's affiliates and associates (i) owns 15% or more of a corporation's voting securities or (ii) is an affiliate or associate of a corporation and was the owner of 15% or more of the corporation's voting securities at any time within the three-year period immediately preceding a business combination of the corporation governed by Section 203. We expect the

existence of this provision to have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. We also anticipate that Section 203 may discourage takeover attempts that might result in a premium over the market price, once a market exists, for the shares of common stock held by our stockholders.

Table of Contents

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Wells Fargo Bank, N.A. The transfer agent's address is Wells Fargo Shareowner Services, 1110 Centre Pointe Curve, Suite 101, Mendota Heights, Minnesota 55120, and its telephone number is (800) 468-9716.

Book Entry; Uncertificated Shares

The common stock sold in any offering pursuant to this prospectus and any accompanying prospectus supplement will be issued in book-entry form through the direct registration system. Under this system, unless a common stockholder requests a physical stock certificate, ownership of our common stock is reflected in account statements periodically distributed to our common stockholders by our transfer agent, who will hold the book-entry shares on behalf of our common stockholders. However, any holder of our common stock who wishes to receive a physical stock certificate evidencing his, her or its shares of our common stock may at any time obtain a stock certificate at no charge by contacting our transfer agent.

New York Stock Exchange Listing

Our common stock is listed on the New York Stock Exchange under the symbol **PBYI**.

Table of Contents

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplement, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the supplement to what extent the general terms and provisions described in this prospectus apply to a particular series of debt securities.

We may issue debt securities either separately, or together with, or upon the conversion or exercise of or in exchange for, other securities described in this prospectus. Debt securities may be our senior, senior subordinated or subordinated obligations and, unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and may be issued in one or more series.

The debt securities will be issued under an indenture between us and Wilmington Trust, National Association, as trustee. We have summarized select portions of the indenture below. The summary is not complete. The form of the indenture has been filed as an exhibit to the registration statement and you should read the indenture for provisions that may be important to you. In the summary below, we have included references to the section numbers of the indenture so that you can easily locate these provisions. Capitalized terms used in the summary and not defined herein have the meanings specified in the indenture.

As used in this section only, Puma, we, our or us refer to Puma Biotechnology, Inc., excluding our subsidiary, unless expressly stated or the context otherwise requires.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in a resolution of our board of directors, in an officer's certificate or by a supplemental indenture. (Section 2.2) The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series (including any pricing supplement or term sheet).

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium, or at a discount. (Section 2.1) We will set forth in a prospectus supplement (including any pricing supplement or term sheet) relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities, if applicable:

the title and ranking of the debt securities (including the terms of any subordination provisions);

the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;

any limit on the aggregate principal amount of the debt securities;

the date or dates on which the principal of the securities of the series is payable;

the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;

the place or places where principal of, and interest, if any, on the debt securities will be payable (and the method of such payment), where the securities of such series may be surrendered for registration of transfer or exchange, and where notices and demands to us in respect of the debt securities may be delivered;

Table of Contents

the period or periods within which, the price or prices at which and the terms and conditions upon which we may redeem the debt securities;

any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities and the period or periods within which, the price or prices at which and in the terms and conditions upon which securities of the series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;

the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;

the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;

whether the debt securities will be issued in the form of certificated debt securities or global debt securities;

the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;

the currency of denomination of the debt securities, which may be United States Dollars or any foreign currency, and if such currency of denomination is a composite currency, the agency or organization, if any, responsible for overseeing such composite currency;

the designation of the currency, currencies or currency units in which payment of principal of, premium and interest on the debt securities will be made;

if payments of principal of, premium or interest on the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;

the manner in which the amounts of payment of principal of, premium, if any, or interest on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index;

any provisions relating to any security provided for the debt securities;

any addition to, deletion of or change in the Events of Default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;

any addition to, deletion of or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;

any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities;

the provisions, if any, relating to conversion or exchange of any debt securities of such series, including if applicable, the conversion or exchange price and period, provisions as to whether conversion or exchange will be mandatory, the events requiring an adjustment of the conversion or exchange price and provisions affecting conversion or exchange;

any other terms of the debt securities, which may supplement, modify or delete any provision of the indenture as it applies to that series, including any terms that may be required under applicable law or regulations or advisable in connection with the marketing of the securities; and

whether any of our direct or indirect subsidiaries will guarantee the debt securities of that series, including the terms of subordination, if any, of such guarantees. (Section 2.2)

Table of Contents

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, or the DTC, or a nominee of the DTC (we will refer to any debt security represented by a global debt security as a book-entry debt security), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a certificated debt security) as set forth in the applicable prospectus supplement. Except as set forth under the heading Global Debt Securities and Book-Entry System below, book-entry debt securities will not be issuable in certificated form.

Certificated Debt Securities. You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. (Section 2.4) No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange. (Section 2.7)

You may effect the transfer of certificated debt securities and the right to receive the principal of, premium and interest on certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

Global Debt Securities and Book-Entry System. Each global debt security representing book-entry debt securities will be deposited with, or on behalf of, the DTC, and registered in the name of the DTC or a nominee of the DTC. Please see Global Securities.

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities. (Article IV)

No Protection in the Event of a Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to any person (a successor person) unless:

we are the surviving corporation or the successor person (if other than Puma) is a corporation organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture; and

Table of Contents

immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing.

Notwithstanding the above, any of our subsidiaries may consolidate with, merge into or transfer all or part of its properties to us. (Section 5.1)

Events of Default

Event of Default means with respect to any series of debt securities, any of the following:

default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of such default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);

default in the payment of principal of any security of that series at its maturity;

default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 60 days after we receive written notice from the trustee or Puma and the trustee receive written notice from the holders of not less than 25% in principal amount of the outstanding debt securities of that series as provided in the indenture;

certain voluntary or involuntary events of bankruptcy, insolvency or reorganization of Puma;

any other Event of Default provided with respect to debt securities of that series that is described in the applicable prospectus supplement. (Section 6.1)

No Event of Default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an Event of Default with respect to any other series of debt securities. (Section 6.1) The occurrence of certain Events of Default or an acceleration under the indenture may constitute an event of default under certain indebtedness of ours or our subsidiaries outstanding from time to time.

We will provide the trustee written notice of any Default or Event of Default within 30 days of becoming aware of the occurrence of such Default or Event of Default, which notice will describe in reasonable detail the status of such Default or Event of Default and what action we are taking or propose to take in respect thereof. (Section 6.1)

If an Event of Default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the

trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt

Table of Contents

securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

The indenture provides that the trustee may refuse to perform any duty or exercise any of its rights or powers under the indenture unless the trustee receives indemnity satisfactory to it against any cost, liability or expense which might be incurred by it in performing such duty or exercising such right or power. (Section 7.1(e)) Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series. (Section 6.12)

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the indenture, unless:

that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and

the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered indemnity or security satisfactory to the trustee, to the trustee to institute the proceeding as trustee, and the trustee has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days. (Section 6.7)

Notwithstanding any other provision in the indenture, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, premium and any interest on that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment. (Section 6.8)

The indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. (Section 4.3) If a Default or Event of Default occurs and is continuing with respect to the securities of any series and if it is known to a responsible officer of the trustee, the trustee shall mail to each Securityholder of the securities of that series notice of a Default or Event of Default within 90 days after it occurs or, if later, after a responsible officer of the trustee has knowledge of such Default or Event of Default. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any Default or Event of Default (except in payment on any debt securities of that series) with respect to debt securities of that series if the trustee determines in good faith that withholding notice is in the interest of the holders of those debt securities. (Section 7.5)

Modification and Waiver

We and the trustee may modify, amend or supplement the indenture or the debt securities of any series without the consent of any holder of any debt security:

to cure any ambiguity, defect or inconsistency;

to comply with covenants in the indenture described above under the heading Consolidation, Merger and Sale of Assets ;

to provide for uncertificated securities in addition to or in place of certificated securities;

to add guarantees with respect to debt securities of any series or secure debt securities of any series;

to surrender any of our rights or powers under the indenture;

to add covenants or events of default for the benefit of the holders of debt securities of any series;

Table of Contents

to comply with the applicable procedures of the applicable depositary;

to make any change that does not adversely affect the rights of any holder of debt securities;

to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;

to effect the appointment of a successor trustee with respect to the debt securities of any series and to add to or change any of the provisions of the indenture to provide for or facilitate administration by more than one trustee; or

to comply with requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act. (Section 9.1)

We may also modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;

reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;

reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;

reduce the principal amount of discount securities payable upon acceleration of maturity;

waive a default in the payment of the principal of, premium or interest on any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);

make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security;

make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, premium and interest on those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or

waive a redemption payment with respect to any debt security. (Section 9.3)

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. (Section 9.2) The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.13)

Table of Contents

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (subject to certain exceptions). We will be so discharged upon the deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money or U.S. government obligations in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred. (Section 8.3)

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

we may omit to comply with the covenant described under the heading "Consolidation, Merger and Sale of Assets" and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and

any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series ("covenant defeasance").

The conditions include:

depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and

delivering to the trustee an opinion of counsel to the effect that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 8.4)

Table of Contents

No Personal Liability of Directors, Officers, Employees or Stockholders

None of our past, present or future directors, officers, employees or stockholders, as such, will have any liability for any of our obligations under the debt securities or the indenture or for any claim based on, or in respect or by reason of, such obligations or their creation. By accepting a debt security, each holder waives and releases all such liability. This waiver and release is part of the consideration for the issue of the debt securities. However, this waiver and release may not be effective to waive liabilities under U.S. federal securities laws, and it is the view of the SEC that such a waiver is against public policy.

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the securities, will be governed by the laws of the State of New York. (Section 10.10)

Table of Contents

DESCRIPTION OF OTHER SECURITIES

We will set forth in the applicable prospectus supplement a description of any warrants or units issued by us that may be offered and sold pursuant to this prospectus.

Table of Contents

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in a prospectus supplement, the securities initially will be issued in book-entry form and represented by one or more global notes or global securities, or, collectively, global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depository, or DTC, and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depository to its nominee or by the nominee to the depository, or by the depository or its nominee to a successor depository or to a nominee of the successor depository.

DTC has advised us that it is:

a limited-purpose trust company organized under the New York Banking Law;

a banking organization within the meaning of the New York Banking Law;

a member of the Federal Reserve System;

a clearing corporation within the meaning of the New York Uniform Commercial Code; and

a clearing agency registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds securities that its participants deposit with DTC. DTC also facilitates the settlement among its participants of securities transactions, such as transfers and pledges, in deposited securities through electronic computerized book-entry changes in participants' accounts, thereby eliminating the need for physical movement of securities certificates. Direct participants in DTC include securities brokers and dealers, including underwriters, banks, trust companies, clearing corporations and other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation, or DTCC. DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others, which we sometimes refer to as indirect participants, that clear through or maintain a custodial relationship with a direct participant, either directly or indirectly. The rules applicable to DTC and its participants are on file with the SEC.

Purchases of securities under the DTC system must be made by or through direct participants, which will receive a credit for the securities on DTC's records. The ownership interest of the actual purchaser of a security, which we sometimes refer to as a beneficial owner, is in turn recorded on the direct and indirect participants' records. Beneficial owners of securities will not receive written confirmation from DTC of their purchases. However, beneficial owners are expected to receive written confirmations providing details of their transactions, as well as periodic statements of their holdings, from the direct or indirect participants through which they purchased securities. Transfers of ownership interests in global securities are to be accomplished by entries made on the books of participants acting on behalf of beneficial owners. Beneficial owners will not receive certificates representing their ownership interests in the global

securities, except under the limited circumstances described below.

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC's partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC's records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers.

Table of Contents

So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depository and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Conveyance of notices and other communications by DTC to direct participants, by direct participants to indirect participants and by direct participants and indirect participants to beneficial owners will be governed by arrangements among them, subject to any legal requirements in effect from time to time.

Redemption notices will be sent to DTC. If less than all of the securities of a particular series are being redeemed, DTC's practice is to determine by lot the amount of the interest of each direct participant in the securities of such series to be redeemed.

Neither DTC nor Cede & Co. (or such other DTC nominee) will consent or vote with respect to the securities. Under its usual procedures, DTC will mail an omnibus proxy to us as soon as possible after the record date. The omnibus proxy assigns the consenting or voting rights of Cede & Co. to those direct participants to whose accounts the securities of such series are credited on the record date, identified in a listing attached to the omnibus proxy.

So long as securities are in book-entry form, we will make payments on those securities to the depository or its nominee, as the registered owner of such securities, by wire transfer of immediately available funds. If securities are issued in definitive certificated form under the limited circumstances described below, we will have the option of making payments by check mailed to the addresses of the persons entitled to payment or by wire transfer to bank accounts in the United States designated in writing to the applicable trustee or other designated party at least 15 days before the applicable payment date by the persons entitled to payment, unless a shorter period is satisfactory to the applicable trustee or other designated party.

Redemption proceeds, distributions and dividend payments on the securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit direct participants' accounts upon DTC's receipt of funds and corresponding detail information from us on the payment date in accordance with their respective holdings shown on DTC records. Payments by participants to beneficial owners will be governed by standing instructions and customary practices, as is the case with securities held for the account of customers in bearer form or registered in street name. Those payments will be the responsibility of participants and not of DTC or us, subject to any statutory or regulatory requirements in effect from time to time. Payment of redemption proceeds, distributions and dividend payments to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC, is our responsibility, disbursement of payments to direct participants is the responsibility of DTC, and disbursement of payments to the beneficial owners is the responsibility of direct and indirect participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as securities depository with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depository is not obtained,

securities certificates are required to be printed and delivered.

Table of Contents

As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;

we determine, in our sole discretion, not to have such securities represented by one or more global securities; or

an Event of Default has occurred and is continuing with respect to such series of securities, we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depository directs. It is expected that these directions will be based upon directions received by the depository from its participants with respect to ownership of beneficial interests in the global securities.

We have obtained the information in this section and elsewhere in this prospectus concerning DTC and DTC's book-entry system from sources that are believed to be reliable, but we take no responsibility for the accuracy of this information.

Table of Contents

PLAN OF DISTRIBUTION

We may sell the offered securities from time to time:

through underwriters or dealers;

through agents;

directly to one or more purchasers; or

through a combination of any of these methods of sale.

We will identify the specific plan of distribution, including any underwriters, dealers, agents or direct purchasers and their compensation in the applicable prospectus supplement.

Table of Contents

LEGAL MATTERS

Latham & Watkins LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Puma Biotechnology, Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements incorporated by reference into this prospectus from Puma Biotechnology, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2013, including schedules appearing therein, and the effectiveness of Puma Biotechnology Inc.'s internal control over financial reporting as of December 31, 2013, have been audited by PKF Certified Public Accountants, A Professional Corporation, independent registered public accounting firm, as set forth in their reports thereon incorporated by reference therein, and incorporated herein by reference. Such consolidated financial statements are, and audited consolidated financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the reports of PKF Certified Public Accountants, A Professional Corporation, pertaining to such consolidated financial statements and the effectiveness of our internal control over financial reporting as of the respective dates (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

Table of Contents

1,000,000 Shares

Puma Biotechnology, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

BofA Merrill Lynch

J.P. Morgan

Citigroup

Leerink Partners

Cowen and Company

, 2015