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

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2016

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number: 001-35703

PUMA BIOTECHNOLOGY, INC.

(Exact name of registrant as specified in its charter)

Delaware	**77-0683487**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

10880 Wilshire Boulevard, Suite 2150
Los Angeles, CA 90024
(424) 248-6500
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $0.0001 per share	The NASDAQ Stock Market LLC (NASDAQ Global Select Market)

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of voting stock held by non-affiliates of the registrant was $505,788,174 as of June 30, 2016, based upon the closing price of $29.79 per share of the registrant's common stock on the New York Stock Exchange (on which the registrant's common stock was then listed) on Thursday, June 30, 2016, the last business day of the registrant's most recently completed second fiscal quarter. Shares of common stock held by each executive officer, director and holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes. As of February 22, 2017, there were 36,951,978 shares of the registrant's common stock outstanding.

Documents Incorporated by Reference:

Portions of the Proxy Statement for the registrant's 2017 Annual Meeting of Stockholders, or the 2017 Proxy Statement, are incorporated by reference into Part III of the Form 10-K to the extent stated herein.

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Any statements about our expectations, beliefs, plans, objectives, assumptions, future events or performance are not historical facts and may be forward looking. 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 anticipated timing of regulatory filings;
- the regulatory approval of our drug candidates;
- the anticipated timing of product revenues and the commercial availability 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 intention and ability to vigorously defend against a securities class action lawsuit, derivative lawsuits and a defamation lawsuit;
- our ability to attract and retain key personnel; and
- our ability to obtain adequate financing.

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. Accordingly, these statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed in them. Discussions containing these forward-looking statements may be found throughout this Annual Report, including the sections entitled “Item 1. Business” and “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations” in Part II of this Annual Report. These forward-looking statements involve risks and uncertainties, including the risks discussed in Part I of this Annual Report, in the section entitled “Item 1A. Risk Factors,” that could cause our actual results to differ materially from those in the forward-looking statements. We undertake no obligation to update the forward-looking statements or to reflect events or circumstances after the date of this document. The risks discussed in this Annual Report should be considered in evaluating our prospects and future financial performance.

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I TEM 1. BUSINESS

Company Overview

Unless otherwise provided in this Annual Report, references to the "Company," "we," "us," and "our" refer to Puma Biotechnology, Inc., a Delaware corporation formed on April 27, 2007 and formerly known as Innovative Acquisitions Corp., together with its wholly-owned subsidiary, Puma Biotechnology Ltd., and all references to "Former Puma" refer to Puma Biotechnology, Inc., a privately-held Delaware corporation formed on September 15, 2010, that merged with and into us in October 2011. We refer to this transaction as the "Merger."

We are a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. We in-license the global development and commercialization rights to three drug candidates—PB272 (neratinib (oral)), PB272 (neratinib (intravenous)) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor, or TKI, that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Currently, we are primarily focused on the development of the oral version of neratinib, and our most advanced drug candidates are directed at the treatment of HER2-positive breast cancer. We believe neratinib has clinical application in the treatment of several other cancers as well, including non-small cell lung cancer, or NSCLC, and other tumor types that over-express or have a mutation in HER2.

Breast cancer is the leading cause of cancer death among women worldwide. 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 trastuzumab (marketed as Herceptin), pertuzumab (marketed as Perjeta) and T-DM1 (marketed as Kadcyla), each produced by Genentech, and lapatinib (marketed as Tykerb) produced by Novartis, 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). 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.

In June and July 2016, we submitted a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, and filed a New Drug Application, or NDA, with the U.S. Food and Drug Administration, or FDA, respectively, for neratinib for the extended adjuvant treatment of patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy. The MAA and NDA submissions are based upon the results of the ExteNET Phase III study, or the ExteNET trial, which reached its primary endpoint whereby neratinib demonstrated a statistically significant reduction in the risk of invasive disease recurrence or death versus placebo. The EMA validated the MAA and the FDA accepted for review the NDA.

Separately, in February 2013, we reached agreement with the FDA under a Special Protocol Assessment, or SPA, for a 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 EMA has also provided follow-on scientific advice, or SA, consistent with that of the FDA regarding our ability to use the trial to support regulatory approval in the European Union. We refer to this trial as PUMA-NER-1301. We initiated this trial in June 2013.

Additionally, in December 2016, we initiated a managed access program for neratinib. Managed access programs provide physicians and patients access to medicines when there are limited or no other therapeutic options available. Our managed access program for neratinib will enable participation from countries outside the United States, including European Union Member States, where permitted by applicable rules, procedures and regulatory authorities. The program will provide access to neratinib for the treatment of early stage HER2-positive breast cancer (extended adjuvant setting), HER2-positive metastatic breast cancer and HER2-mutated solid tumors. Patients must not be able to participate in any ongoing neratinib clinical trial to qualify for our managed access program. Patients in the managed access program will be given neratinib and will be instructed to take a prophylaxis during treatment to manage neratinib-related diarrhea, which we expect will consist of high dose loperamide and budesonide. We have partnered with Caligor Opco LLC, which specializes in early access to medicines, to implement and oversee the managed access program for neratinib.

In addition to continuing to follow the patients from the ExteNET trial and continuing the PUMA-NER-1301 trial, we are actively conducting the following trials to evaluate the safety and efficacy of neratinib in various indications:

- a Phase II clinical trial of neratinib for the extended adjuvant treatment of patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab (Herceptin)-based therapy in which patients are given antidiarrheal prophylaxis including loperamide alone or in combination with budesonide or other agents in order to prevent and reduce the neratinib-related diarrhea;

- a Phase II clinical trial of neratinib in combination with the chemotherapy drug capecitabine in patients with HER2-positive metastatic breast cancer that has metastasized to the brain;
- a Phase II clinical trial of neratinib in combination with the endocrine therapy fulvestrant in the treatment of patients with HER2-negative breast cancer that have a HER2 mutation;
- a Phase II clinical trial of neratinib monotherapy in the treatment of solid tumors that have an activating HER2 mutation;
- Phase II clinical trials in the neoadjuvant treatment of HER2-positive breast cancer;
- a Phase II clinical trial in the treatment of HER2-mutated non-small cell lung cancer; and
- a Phase I/II trial of neratinib plus Kadcyla in patients with metastatic HER2-positive breast cancer.

During the next 12 to 18 months, we expect to commence a Phase II clinical trial for the neoadjuvant treatment of patients with triple negative breast cancer who have phosphorylated HER1 (EGFR) and HER2 and a Phase II randomized trial of neratinib plus endocrine in patients with hormone receptor-positive HER2-positive metastatic breast cancer. We also plan to 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.

We license the commercial rights to our current drug candidates from Pfizer, Inc., which had previously been responsible for the clinical trials regarding neratinib. Going forward, we expect to augment our product pipeline by acquiring, through license or otherwise, additional drug candidates for research and development and potential commercialization. In evaluating potential drug candidates, we employ disciplined decision criteria that favor drug candidates that have undergone at least some clinical study. Our decision to acquire a drug candidate will also depend on our evaluation of the scientific merits of the underlying technology, the costs of the transaction and other economic terms of any proposed license, the amount of capital that we anticipate will be required to develop the drug candidate and the economic potential of the drug candidate if approved for commercialization. We believe this strategy minimizes our clinical development risk and allows us to accelerate the development and potential commercialization of current and future drug candidates.

Strategy

Our strategy is to become a leading oncology-focused biopharmaceutical company. The key elements of our strategy are as follows:

- *Seek regulatory approval and commence commercialization of neratinib in our lead indication* . In June and July 2016, we submitted an MAA to the EMA and filed an NDA with the FDA, respectively, for neratinib for the extended adjuvant treatment of patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy. The MAA and NDA submissions are based upon the results of the ExteNET trial, which reached its primary endpoint whereby neratinib demonstrated a statistically significant reduction of risk of invasive disease recurrence or death versus placebo. We are continuing to evaluate potential commercialization options for the extended adjuvant setting, including developing a direct sales force, contracting with third parties to provide sales and marketing capabilities, some combination of these two options or other strategic options. Additionally, we believe we currently have sufficient inventory on hand to support at least the first year of commercialization in the extended adjuvant setting and will continue to monitor and evaluate our third party manufacturers' ability to provide commercial supply of the product.
- *Continue to advance the development of neratinib for the treatment of other HER2-positive breast cancer indications.* We are primarily focused on developing neratinib for the treatment of patients with HER2-positive breast cancer, HER2-negative breast cancer who have a HER2 mutation and other solid tumors with an activating mutation in HER2, and HER2-mutated non-small cell lung cancer. In addition to our completed ExteNET trial, we have several ongoing clinical trials focused on the treatment of patients with HER2-positive breast cancer. In June 2013, we commenced a Phase III clinical trial of neratinib in patients with HER2-positive metastatic breast cancer who have failed two or more prior treatments (third-line disease). We also have several ongoing Phase I and Phase II clinical trials evaluating the use of neratinib in combination with various other drugs, including Kadcyla, Xeloda, Paclitaxel and Torisel, to treat patients with HER2-positive metastatic breast cancer and HER2-positive metastatic breast cancer that has metastasized to the brain.
- *Expand our product pipeline by pursuing additional applications of neratinib.* We believe there are additional applications for neratinib in the treatment of HER2-mutated non-small cell lung cancer, which we also believe may be underserved by current treatment alternatives; in the treatment of patients with HER2-negative breast cancer who have a HER2 mutation; and in tumor types where HER2 is over-expressed or mutated. We intend to further evaluate the safety and efficacy of neratinib for treating these cancers.

- *Build a sustainable product pipeline by employing multiple therapeutic approaches and disciplined decision criteria based on clearly defined proof of principal goals.* We seek to build a sustainable product pipeline by employing multiple therapeutic approac hes and by acquiring drug candidates belonging to known drug classes. In addition, we employ disciplined decision criteria to assess drug candidates, favoring drug candidates that have undergone at least some clinical study. Our decision to license a drug candidate will also depend on the scientific merits of the technology; the costs of the transaction and other economic terms of the proposed license; the amount of capital required to develop the technology; and the economic potential of the drug candidate , should it be commercialized. We believe this strategy minimizes our clinical development risk and allows us to accelerate the development and potential commercialization of current and future drug candidates. We intend to pursue regulatory approval for a majority of our drug candidates in multiple indications.
- *Evaluate the commercialization strategies on a product-by-product basis in order to maximize the value of each.* As we move our drug candidates through development toward regulatory approval, we plan to evaluate several options for each drug candidate's commercialization strategy. These options include building our own internal sales force; entering into a joint marketing partnership with another pharmaceutical or biotechnology company, whereby we jointly sell and market the product; and out-licensing our product, whereby another pharmaceutical or biotechnology company sells and markets our product and pays us a royalty on sales. Our decision may be different for each product that reaches commercialization and will be based on a number of factors including capital necessary to execute on each option, size of the market to be addressed and terms of potential offers from other pharmaceutical and biotechnology companies.

Breast Cancer Overview

Breast cancer is the leading cause of cancer death among women worldwide, with approximately 1 million new cases reported each year and more than 400,000 deaths per year. Approximately 20% to 25% of breast cancer tumors show over-expression of the HER2 protein. Women with breast cancer that over-expresses HER2 are at greater risk for disease progression and death than women whose tumors do not over-express HER2. Therapeutic strategies have been developed to block HER2 in order to improve the treatment of this cancer.

Trastuzumab, pertuzumab, lapatinib and T-DM1 are all drugs that bind to the HER2 protein and thereby cause the cells to cease reproducing. Today, these drugs are used as single agents, in combination with other drugs and in combination with chemotherapy to treat patients with HER2-positive breast cancer at various stages.

Currently, the only treatment approved by the FDA for the treatment of neoadjuvant (newly diagnosed) HER2-positive breast cancer is the combination of pertuzumab plus trastuzumab and taxane chemotherapy. The FDA-approved therapy for the adjuvant treatment of HER2-positive early stage breast cancer is the combination of trastuzumab and chemotherapy. In addition, we are aware of the ongoing APHINITY trial, which is comparing pertuzumab plus trastuzumab and chemotherapy versus placebo plus trastuzumab and chemotherapy as an adjuvant therapy, and the KAITLIN trial, which is comparing trastuzumab plus pertuzumab plus taxane following anthracyclines versus T-DM1 plus pertuzumab following anthracyclines as an adjuvant therapy. There is currently no FDA-approved drug for the extended adjuvant treatment of early stage HER2-positive breast cancer that has been previously treated with trastuzumab.

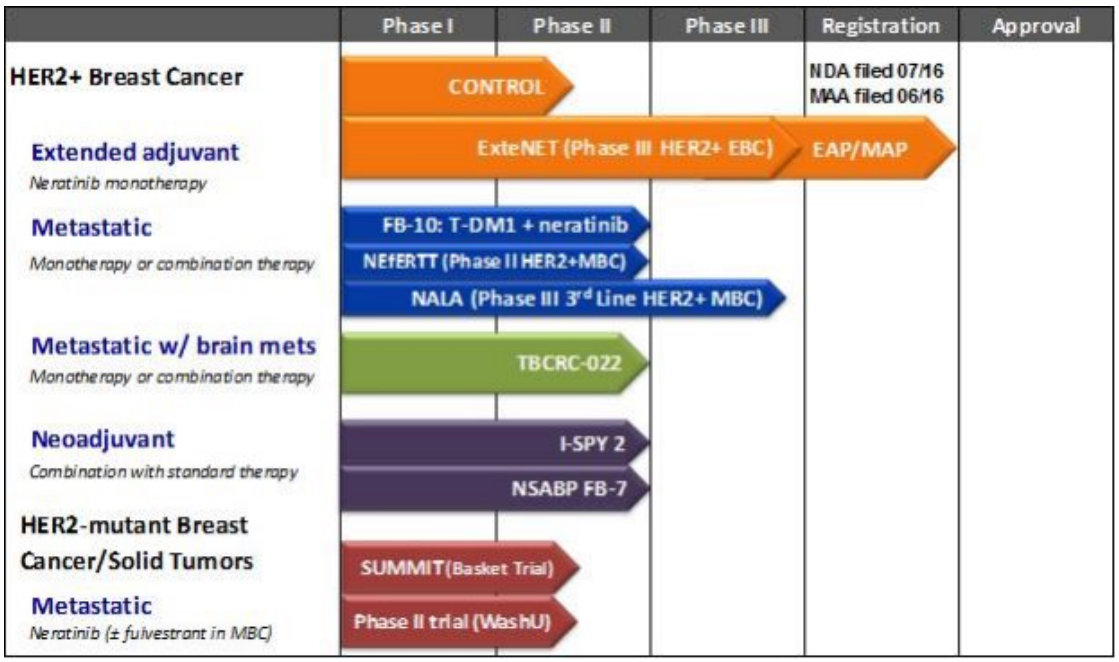
Trastuzumab and pertuzumab given in combination with taxane chemotherapy is the current first-line standard of care for HER2-positive metastatic breast cancer. Lapatinib (Tykerb), given in combination with the chemotherapy drug capecitabine, is also FDA-approved for the treatment of patients who have failed prior treatments. In a Phase II clinical trial, lapatinib demonstrated a median progression free survival of 8 to 9 weeks and a response rate of 5 - 7%. In a Phase III clinical trial, patients with HER2-positive metastatic breast cancer who received the combination of lapatinib plus capecitabine demonstrated a median progression free survival of 27.1 weeks and a response rate of 23.7%. In the Phase III EMILIA trial, the combination of lapatinib plus capecitabine demonstrated a median progression free survival of 25.6 weeks and a response rate of 30.8%. T-DM1 is approved by the FDA for the treatment of patients with HER2-positive metastatic breast cancer who previously received first line trastuzumab based therapy. Unfortunately, the disease eventually progresses for most patients with HER2-positive breast cancer while on these treatments. For these reasons, there is a need for alternatives to block HER2 signaling in patients who fail treatment with prior HER2 directed treatments. Neratinib is an orally active small molecule that inhibits HER2 at a different site and uses a different mechanism than trastuzumab. As a result, we believe that neratinib may have utility in patients with HER2-positive metastatic breast cancer who have failed treatment with trastuzumab.

We believe that there are approximately 36,000 patients in the United States and 34,000 patients in the European Union, or EU, with newly diagnosed HER2-positive breast cancer. Based on our internal estimates, we believe that the worldwide Herceptin adjuvant revenue was approximately $4.5 to $5.0 billion in 2015. We also believe that there are between 5,000 and 6,000 patients in the United States with third-line or later HER2-positive metastatic breast cancer. In 2013, worldwide sales of Tykerb for this indication were approximately $325 million.

We believe that approx imately 2% of all newly diagnosed breast cancer patients have mutation in HER2 kinase (approximately 4,000 to 5,000 patients in the United States) and that approximately 4 – 5% of all metastatic breast cancer patients have mutation in HER2 kinase (approxim ately 8,000 to 10,000 patients in the United States). We believe that this mutation occurs mostly in patients with hormone receptor-positive disease.

Product Development Pipeline

The following chart shows each of our current drug candidates and their clinical development stage.



Neratinib

Neratinib is a potent irreversible tyrosine kinase inhibitor, or TKI, that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Based on pre-clinical studies and clinical trials to date, we believe that neratinib may offer an advantage over existing treatments that are used in the treatment of patients with HER2-positive metastatic breast cancer who have failed prior treatments, including treatment with trastuzumab, pertuzumab, and T-DM1. Currently, the treatment of metastatic breast cancer patients involves treatment with these agents either alone or in combination with chemotherapy. We believe that by more potently inhibiting HER2 at a different site and acting via a mechanism different from other agents, neratinib may have therapeutic benefits in patients who have failed these existing treatments, most notably due to its increased selectivity and irreversible inhibition of the HER2 target enzyme.

In addition, we believe neratinib has clinical application in the treatment of other cancers, including non-small cell lung cancer and other tumor types that over-express or have a mutation in HER2.

Our initial focus is on the development of the oral formulation of neratinib. We are also evaluating for potential development an intravenous formulation of neratinib and PB357, a back-up compound to neratinib.

PB272 (neratinib (oral))—Early Stage Breast Cancer

Extended Adjuvant Breast Cancer

Two-Year ExteNET Data. In July 2014, we announced top line results from the Phase III clinical trial of neratinib for the extended adjuvant treatment of early stage HER2-positive breast cancer (ExteNET Trial). The data from this trial was presented in an oral presentation at the American Society of Clinical Oncology (ASCO) 2015 Annual Meeting in June 2015 and was published online in *The Lancet Oncology* in February 2016. 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 2,840 patients in 41 countries with 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 safety results of the study showed that the most frequently observed adverse event for the neratinib-treated patients was diarrhea, with approximately 39.9% of the neratinib-treated patients experiencing grade 3 or higher diarrhea (1 patient, 0.1%, had grade 4 diarrhea). Patients who received neratinib in this trial did not receive any prophylaxis with antidiarrheal agents to prevent the neratinib-related diarrhea. Puma's previously reported clinical data from several trials have demonstrated that the use of high dose prophylactic loperamide may greatly reduce the rate of grade 3 diarrhea with neratinib, with grade 3 diarrhea rates ranging from 0-17% in studies in which high dose loperamide prophylaxis was used. We are currently conducting an international, open-label, Phase II study investigating the use of antidiarrheal prophylaxis with loperamide alone or with other agents in the prevention and reduction of neratinib-associated diarrhea and more specifically grade 3 diarrhea. The interim results of this trial (data cut-off of November 2016) showed that the incidence of grade 3 diarrhea for the total 135 patients who received the loperamide prophylaxis was 28.1% and that the incidence of grade 3 diarrhea was 15.0% for the 40 patients who received the combination of loperamide plus budesonide. In all of its current ongoing studies Puma is instituting the use of antidiarrheal prophylaxis for the first cycle of treatment in order to continue to reduce the neratinib-related diarrhea. See "– *Safety Database* " for additional information.

The primary endpoint of the trial was invasive disease-free survival (DFS). The results of the trial demonstrated that treatment with neratinib resulted in a 33% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.67, p = 0.009). The 2-year DFS rate for the neratinib arm was 93.9% and the 2-year DFS rate for the placebo arm was 91.6%. 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% reduction of risk of disease recurrence including DCIS or death versus placebo (hazard ratio = 0.63, p = 0.002). The 2-year DFS-DCIS rate for the neratinib arm was 93.9% and the 2-year DFS-DCIS rate for the placebo arm was 91.0%.

As an inclusion criteria for the ExteNET trial, patients needed to have tumors that were HER2-positive using local assessment. In addition, as a pre-defined subgroup in the trial, patients had centralized HER2 testing performed on their tumor as well. At the time the 2-year data was compiled, centralized HER2 testing had been performed on 1,704 (60%) of the patients in the ExteNET trial and further central testing on available samples was currently ongoing. For the 1,463 patients whose tumors were HER2-positive by central confirmation, the results of the trial demonstrated that treatment with neratinib resulted in a 49% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.51, p = 0.002). The 2-year DFS rate for the centrally confirmed patients in the neratinib arm was 94.7% and the 2-year DFS rate for the centrally confirmed patients in the placebo arm was 90.6%. For the patients in the trial whose tumors were HER2-positive by central confirmation, the results of the trial demonstrated that treatment with neratinib resulted in a 51% reduction of risk of disease recurrence including DCIS or death versus placebo (hazard ratio = 0.49, p < 0.001). The 2-year DFS-DCIS rate for the centrally confirmed patients in the neratinib arm was 94.7% and the 2-year DFS rate for centrally confirmed patients in the placebo arm was 90.2%.

For the pre-defined subgroup of patients with hormone receptor positive disease, the results of the trial demonstrated that treatment with neratinib resulted in a 49% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.51, p = 0.001). The 2-year DFS rate for the neratinib arm was 95.4% and the 2-year DFS rate for the placebo arm was 91.2%. For the patients in the trial whose tumors were HER2-positive by central confirmation, the results of the trial demonstrated that treatment with neratinib resulted in a 75% reduction of risk of invasive disease recurrence or death (hazard ratio = 0.25, p < 0.001). The 2-year DFS rate for the centrally confirmed patients in the neratinib arm was 97.0% and the 2-year DFS rate for centrally confirmed patients in the placebo arm was 88.4%.

Based on the results from the ExteNET trial, in June and July 2016, we submitted an MAA with the EMA and filed an NDA with the FDA, respectively, for regulatory approval of neratinib in the extended adjuvant setting.

Five-Year ExteNET Data. In July 2016, we announced updated results from the ExteNET trial. As part of the data analysis for the NDA filing in the United States and the MAA submission in Europe, an updated analysis that included an interim 5-year invasive DFS analysis was performed. This data analysis was performed in order to examine the durability of treatment effect beyond the 2-year data included in the primary analysis. This interim analysis was not a pre-planned analysis in the statistical analysis pl an for the trial. For the primary endpoint of the trial, invasive DFS, the 5-year interim results of the trial demonstrated that treatment with neratinib resulted in a 26% reduction of risk of invasive disease recurrence or death versus placebo (hazard rat io = 0.74, p = 0.017). The 5-year interim invasive DFS rate for the neratinib arm was 90.4% and the 5-year interim invasive DFS rate for the placebo arm was 87.9%. Additional updated results for the 3-year invasive DFS rate and 4-year invasive DFS rate are shown in the table below:

DFS for Intent to Treat (ITT) Population			
	3-Year DFS	4-Year DFS	5-Year Interim DFS
Neratinib	92.5%	91.4%	90.4%
Placebo	90.3%	89.2%	87.9%
Absolute Invasive DFS Difference	2.2%	2.2%	2.5%

As an inclusion criteria for the ExteNET trial, patients needed to have tumors that were HER2 positive using local assessment. In addition, as a pre-defined subgroup in the trial, patients had centralized HER2 testing performed on their tumor as well. To date, centralized HER2 testing has been performed on 2,140 (75%) of the patients in the ExteNET trial, and further centralized testing on available samples is currently ongoing. For the 1,777 patients whose tumors were HER2 positive by central confirmation, the interim results of the trial demonstrated that treatment with neratinib resulted in a 30% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.70, p = 0.026). The 5-year interim invasive DFS rate for the centrally confirmed patients in the neratinib arm was 90.8% and the 5-year interim invasive DFS rate for the centrally confirmed patients in the placebo arm was 88.1%.

For the pre-defined subgroup of 1,631 patients with hormone receptor positive disease, the interim results of the trial demonstrated that treatment with neratinib resulted in a 41% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.59, p = 0.002). The 5-year interim invasive DFS rate for the neratinib arm was 91.7% and the 5-year interim invasive DFS rate for the placebo arm was 86.9%. Additional updated results for the 3-year invasive DFS rate and 4-year invasive DFS rate are shown in the table below:

DFS for Hormone Receptor Positive (HR-positive) Population			
	3-Year DFS	4-Year DFS	5-Year Interim DFS
Neratinib	93.8%	92.9%	91.7%
Placebo	89.9%	88.6%	86.9%
Absolute Invasive DFS Difference	3.9%	4.3%	4.8%

We anticipate that full 5-year DFS data will be available in the second half of 2017.

Neoadjuvant Breast Cancer

At the 2010 CTRC-AACR San Antonio Breast Cancer Symposium, the results of the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Study, or the Neo-ALTTO study, were presented. In this trial, patients with HER2-positive breast cancer were randomized to receive either the combination of paclitaxel plus trastuzumab, the combination of paclitaxel plus lapatinib or the combination of paclitaxel plus trastuzumab plus lapatinib, as a neoadjuvant (preoperative) therapy. The results of the trial demonstrated that patients who received the combination of paclitaxel plus trastuzumab demonstrated a pathological complete response rate, or pCR, of 27.6% in the breast and lymph nodes, the patients who received paclitaxel plus lapatinib had a pCR of 20.0% and the patients who received the combination of paclitaxel plus trastuzumab plus lapatinib had a pCR of 46.8%.

Also at the 2010 CTRC-AACR San Antonio Breast Cancer Symposium, the results of the Neo-Sphere study were presented. In this trial, patients with HER2-positive breast cancer were randomized to receive either the combination of docetaxel plus trastuzumab, the combination of docetaxel plus pertuzumab, the combination of trastuzumab plus pertuzumab or the combination of docetaxel plus trastuzumab plus pertuzumab, as a neoadjuvant (preoperative) therapy. The results of the trial demonstrated that the patients who received the combination of docetaxel plus trastuzumab had a pCR of 21.5%in the breast and lymph nodes, the patients who received docetaxel plus pertuzumab had a pCR of 17.7%, the patients who received pertuzumab plus trastuzumab had a pCR of 11.2% and the patients who received the combination of docetaxel plus trastuzumab plus pertuzumab had a pCR of 39.3%.

I-SPY 2 Trial. In 2010, the Foundation for the National Institutes of Health initiated the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2). The I-SPY 2 TRIAL 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 pCR in the breast and the lymph nodes at the time of surgery. The goal of the trial is to match investigational regimens with patient subsets on the basis of molecular characteristics, referred to as biomarker signatures that, ben efit from the regimen.

The I-SPY 2 TRIAL involved an adaptive trial design based on Bayesian predictive probability that a regimen will be shown to be statistically superior to standard therapy in an equally randomized 300-patient confirmatory trial. Regimens that have a high Bayesian predictive probability of showing superiority in at least one of 10 predefined signatures graduate from the trial. Regimens are dropped for futility if they show a low predictive probability of showing superiority over standard therapy in all 10 signatures. A maximum total of 120 patients can be assigned to each experimental regimen. A regimen can graduate early and at any time after having 60 patients assigned to it.

In April 2014, we announced the results for the neratinib-containing regimen of the I-SPY 2 TRIAL. 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 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-SPY 2 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 I-SPY 1) 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 whom 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%.

The results of the I-SPY2 TRIAL with neratinib were published in *The New England Journal of Medicine* in July 2016. Based on the graduation of neratinib from the I-SPY2 TRIAL, neratinib is now eligible to proceed into the I-SPY 3 Phase III clinical trial, which is currently being planned.

FB-7 Trial. In 2010, Pfizer, in collaboration with the National Surgical Adjuvant Breast and Bowel Project, or NSABP, a clinical trials cooperative group supported by the National Cancer Institute, or NCI, initiated the FB-7 study to investigate the use of neratinib as a neoadjuvant therapy for newly diagnosed HER2-positive breast cancer. In this trial, a total of 126 patients are randomized to receive neratinib plus the chemotherapy drug paclitaxel or trastuzumab plus paclitaxel prior to having surgery to remove their tumors. The purpose of this study is to test whether adding neratinib to paclitaxel chemotherapy is better than trastuzumab plus paclitaxel chemotherapy before having surgery. This trial was modified in 2012 to include a third treatment arm where patients will receive the combination of neratinib plus trastuzumab plus paclitaxel prior to having surgery to remove their tumors.

Data from this trial were presented at the 2015 CTRC-AACR San A ntonio Breast Cancer Symposium. Patients were randomly assigned to trastuzumab (T) or neratinib (N) or the combination (T+N) with weekly paclitaxel (P) followed by standard doxorubicin and cyclophosphamide chemotherapy (AC) administered prior to surgery. 126 U.S., Canadian, and European patients were randomly assigned to Arm 1 (T+P followed by AC), Arm 2 (N+P followed by AC) or Arm 3 (T+N+P followed by AC). The primary endpoint of the trial was pathological complete response rate (pCR) in the breast and lymph nodes. Tumor tissue was collected on patients at the time of diagnosis. This tissue will be analyzed for several biomarkers including AKT, cMET, EGFR, ESR-alpha, HER2, HER3, HER4, p95 HER2 and PI3K and intrinsic subtypes. A key secondary endpoint of this trial is the molecular and genetic correlates of response for each of these biomarkers.

For the intent-to-treat patient population (hormone receptor positive (HR+) and hormone receptor negative (HR-)), the pCR rate for Arm 1 was 38.1%, for Arm 2 was 33.3% and for Arm 3 was 50.0%. For the HR+ patients, the pCR rate for Arm 1 was 29.6%, for Arm 2 was 27.6% and for Arm 3 was 30.4%. For the HR- patients, the pCR rate for Arm 1 was 57.1%, for Arm 2 was 46.2% and for Arm 3 was 73.7%.

The most frequently observed severe adverse event in the two neratinib treated arms of the trial (Arm 2 and Arm 3) was diarrhea. In the first 19 patients treated in Arm 2 of the trial, high dose loperamide (16 mg per day initially) as primary prophylaxis was not given to prevent the neratinib-related diarrhea. In this subset of patients the grade 3 diarrhea rate was 42% (8/19). In the next 10 patients treated in Arm 2 and the first 20 patients treated in Arm 3, high dose primary prophylaxis (16 mg per day initially) with loperamide was given during the initial two weeks of the first cycle of treatment. Using two weeks of intensive loperamide prophylactically, the grade 3 diarrhea rate in Arm 2 was 30% (3/10) and the grade 3 diarrhea rate in Arm 3 was 35% (7/20). In the next 13 patients in Arm 2 and 22 patients in Arm 3, high dose prophylaxis (16 mg per day initially) was given for the entire first cycle of treatment (4 weeks). The grade 3 diarrhea rate was 15% (2/13) in Arm 2 and 23% (5/22) in Arm 3.

In December 2016, a biomarker analysis of the FB-7 trial was presented at the 2016 CTRC-AACR San Antonio Breast Cancer Symposium (SABCS). Pre-treatment core biopsy samples (n=59) and post treatment surgical samples (n=17) were obtained from a subset of patients treated in the FB-7 trial. pCR data were available for 51 patients from the biomarker cohort. After excluding low tumor content non-evaluable samples, correlative biomarker analysis was performed in 42 patients.

Expression levels and the activation status of EGFR/HER2 signaling proteins were investigated. The results of the phosphorylated HER2 (phosphoHER2) showed that median levels of phosphoHER2 were higher in the patients who achieved a pCR with neratinib (n=7) than in the patients who did not achieve a pCR who received either trastuzumab (n=8, p=0.07) or the combination of trastuzumab plus neratinib (n=4, p=0.035). There was not a significant difference in the median levels of phosphoHER2 in the patients who achieved a pCR with neratinib (n=7), trastuzumab (n=8, p=0.16) or the combination of trastuzumab plus neratinib (n=4, p=0.10).

The truncated form of HER2 known as p95HER2 was measured by the proprietary assay of Pierian Bioscience. p95HER2 represents a truncated form of the HER2 receptor that lacks the extracellular trastuzumab binding domain. It is believed to represent a mechanism of trastuzumab resistance. Median p95HER2 levels were higher in samples from patients who achieved a pCR with neratinib than in the patients who did not achieve a pCR and who received either trastuzumab (p=0.027) or the combination of trastuzumab plus neratinib (p=0.009). There was not a significant difference in the median levels of p95HER2 in the patients who achieved a pCR with neratinib (n=7), trastuzumab (n=8, p=0.16) or the combination of trastuzumab plus neratinib (n=4, p=0.35).

The MammaPrint assay was performed on 59 samples to determine if there was any imbalance between arms. This assay is a genomic test that analyzes the activity of 70 genes and then calculates a recurrence score that is either low risk or high risk. The results of the MammaPrint showed that the patients in all three arms of the FB-7 trial were balanced with the median MammaPrint risk score being similar across arms. There were only three patients with a MammaPrint low score.

PB272 (neratinib (oral))—Metastatic Breast Cancer

Trials of Neratinib as a Single Agent . In 2009, Pfizer presented data at the CTRC-AACR San Antonio Breast Cancer Symposium from a Phase II trial of neratinib administered as a single agent to patients with HER2-positive metastatic breast cancer. Final results from this trial were published in the Journal of Clinical Oncology in March 2010.

The trial involved a total of 136 patients, 66 of whom had received prior treatment with trastuzumab and 70 of whom had not received prior treatment with trastuzumab. The results of the study showed that neratinib was reasonably well-tolerated among both the pretreated patients and the patients who had not received prior treatment with trastuzumab. Diarrhea was the most common side effect, but was manageable with antidiarrheal agents and dose modification. Efficacy results from the trial showed that the objective response rate was 24% for patients who had received prior trastuzumab treatment and 56% for patients with no prior trastuzumab treatment. Furthermore, the median PFS was 22.3 weeks for the patients who had received prior trastuzumab and 39.6 weeks for the patients who had not received prior trastuzumab.

Trials of Neratinib in Combination with Other Anti-Cancer Drugs . In November 2014, we announced top line results from a Phase II clinical trial of ner atinib for the treatment of first-line HER2-positive locally recurrent or metastatic breast cancer (NEfERTT trial). Data from this trial was presented at the American Society of Clinical Oncology (ASCO) 2015 Annual Meeting in June 2015. 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 pati ents 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 neratini b or paclitaxel plus trastuzumab. The primary endpoint of the trial was progression free survival. The secondary endpoints of the study included objective response rate and the incidence of central nervous system (CNS) metastases, including brain metastase s.

The results of the trial demonstrated that the progression free survival for the patients who received the combination of paclitaxel plus neratinib was 12.9 months and the progression free survival for the patients who received the combination of paclitaxel plus trastuzumab was 12.9 months (p=0.777). 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 77.6% (p=0.522). 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% reduction in the incidence of CNS metastases compared to the incidence of CNS metastases in patients who received the combination of paclitaxel plus trastuzumab. Symptomatic or progressive CNS recurrences occurred in 20 patients (8.3%) in the neratinib-paclitaxel group and 41 patients (17.3%) in the trastuzumab-paclitaxel group (relative risk 0.48, p=0.002). The estimated Kaplan-Meier 2-year incidence of CNS recurrences was 16.3% in the neratinib-paclitaxel group and 31.2% in the trastuzumab-paclitaxel group (hazard ratio 0.45, p=0.004). 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. The Phase II trial results were published online in the *JAMA Oncology* in April 2016 .

Pfizer presented data from a Phase II trial at the 2010 CTRC-AACR San Antonio Breast Cancer Symposium, which evaluated the safety and efficacy of neratinib when given in combination with the anti-cancer drug vinorelbine in patients with HER2-positive metastatic breast cancer. In the 56 patients who had not been previously treated with the anti-HER2 therapy lapatinib, treatment with the combination of vinorelbine plus neratinib resulted in an overall response rate of 57% and PFS was 44.1 weeks. For those patients who had received prior treatment with lapatinib, the overall response rate was 50%. The combination of vinorelbine and neratinib was generally well tolerated.

Data from a third Phase II study, in which patients with confirmed HER2-positive metastatic breast cancer who had failed treatment with trastuzumab and taxane chemotherapy were given neratinib in combination with capecitabine, was presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium. The results of the study showed that the combination of PB272 and capecitabine had acceptable tolerability. The efficacy results from the trial showed that for the 61 patients in the trial who had not been previously treated with the HER2 targeted anti-cancer drug lapatinib, there was an overall response rate of 64% and a clinical benefit rate of 72%. In addition, for the seven patients in the trial who had previously been treated with lapatinib, there was an overall response rate of 57% and a clinical benefit rate of 71%. The median PFS for patients who had not received prior treatment with lapatinib was 40.3 weeks and the median PFS for the patients who had received prior lapatinib treatment was 35.9 weeks.

In February 2013, we reached agreement with the FDA under an SPA, for our planned Phase III clinical trial of neratinib in patients with HER2-positive metastatic breast cancer who have failed two or more prior treatments (third-line disease). The SPA is a written agreement between us, as the trial's sponsor, and the FDA regarding the design, endpoints, and planned statistical analysis of the Phase III trial with respect to the effectiveness of PB272 for the indication to be studied to support a New Drug Application, or NDA. The EMA has also provided follow-on 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 an MAA in the EU.

Pursuant to the SPA and SA, the Phase III trial is designed as a randomized study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with third-line HER2-positive metastatic breast cancer. The trial is expected to enroll approximately 600 patients who will be randomized (1:1) to receive either PB272 plus capecitabine or lapatinib plus capecitabine. The trial will be conducted at approximately 250 sites in North America, Europe and Asia-Pacific. The agreed upon co-primary endpoints of the trial are PFS and overall survival. Our plan is to use the PFS data from the trial as the basis for submission of an NDA, and its foreign equivalents for Accelerated/Conditional Approval for PB272 from the regulatory agencies. We commenced patient enrollment in this Phase III trial in the second quarter of 2013.

In 2010, Pfizer also initiated a Phase I/II trial of neratinib in combination with the anti-cancer drug temsirolimus, or Torisel, in patients with HER2-positive metastatic breast cancer who have failed multiple pri or treatments. The trial was conducted as a Phase I/II trial of PB272 given in combination with the anticancer drug temsirolimus in patients with HER2-positive metastatic breast cancer. The Phase I portion of the trial, which was reported previously, deter mined that the maximum tolerated dose was 240 mg of neratinib daily with 8 mg of temsirolimus weekly and the dose limiting toxicity was diarrhea. The interim Phase II data was presented at the 2014 CTRC-AACR San Antonio Breast Cancer Symposium. The Phase II portion of the study was conducted in two cohorts. The first cohort, referred to as the Maximum Tolerated Dose (MTD) cohort, received 240 mg of neratinib daily with 8 mg of temsirolimus weekly. This cohort of patients received low dose loperamide (4 mg per day) prophylactically in order to reduce the neratinib-related diarrhea. The second cohort of patients, referred to as the Dose Escalation cohort (DE cohort), received 240 mg of neratinib daily and initially received 8 mg of temsirolimus weekly. This c ohort of patients received high dose loperamide (16 mg per day initially) prophylactically in order to reduce the neratinib-related diarrhea. If patients in the DE cohort had no tolerability issues with the combination of neratinib and temsirolimus given a t 8 mg per week during the first cycle of treatment, patients in this DE cohort were allowed to dose escalate the temsirolimus to 15 mg per week for the remainder of the study. Patients in both cohorts in the study received a median of 3 prior regimens in the metastatic setting (range 1-8 prior regimens) before entering the trial. The 37 patients in the MTD cohort were enrolled at 3 centers in the United States and the 45 patients in the DE cohort were enrolled at 8 centers in the United States, Europe and Asia. The interim safety results of the study showed that the most frequently observed adverse event for the patients who received the combination of neratinib plus temsirolimus was diarrhea. For the 37 patients in the MTD cohort, who received low dose lo peramide prophylactically, 12 patients (32%) experienced grade 3 diarrhea. For the 41 patients in the DE cohort, who received high dose loperamide prophylactically and were allowed to dose escalate the temsirolimus dose, 7 patients (17%) reported grade 3 d iarrhea. 4 (57%) of the 7 patients in the DE cohort who experienced grade 3 diarrhea were not compliant with the high dose loperamide prophylaxis. There were 4 patients in the DE cohort who did not yet have safety data reported and are therefore not includ ed in the safety population. For the patients in the DE cohort, thus far 47% of the patients have been able to dose escalate from 8 mg per week of temsirolimus to 15 mg per week of temsirolimus. The interim efficacy results from the trial showed that for the 37 patients in the MTD cohort, 11 patients (30%) experienced a partial response (PR). The median duration of response for this cohort of patients was 3.0 months and the median progression-free survival was 4.8 months. For the 37 evaluable patients in t he DE cohort, the efficacy results from the trial demonstrated that 11 patients (30%) experienced a partial response (PR). The median duration of response for this cohort of patients was 7.4 months and the median progression free survival is not yet mature . As of December 2014, there were a total of 18 patients currently on active treatment in the trial. 8 of the 17 active patients in the DE cohort have not yet had tumor assessments.

Metastatic Breast Cancer with Brain Metastases

Approximately one-third of the patients with HER2-positive metastatic breast cancer develop metastases that spread to their brain. The current antibody-based treatments, including trastuzumab, pertuzumab and T-DM1, do not enter the brain and therefore are not believed to be effective in treating these patients. In a Phase II trial with lapatinib given as a single agent, lapatinib demonstrated a 6% objective response rate in the patients with HER2-positive metastatic breast cancer whose disease spread to their brain. In January 2012, a Phase II trial of neratinib as a single agent and in combination with the anticancer drug capecitabine in patients with HER2-positive metastatic breast cancer that has spread to their brain was initiated in conjunction with the Dana Farber Translational Breast Cancer Research Consortium. In June 2014, at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting, results from the first cohort (n=40) who were administered neratinib monotherapy was presented. The efficacy results from the first cohort of the trial showed that for the 40 evaluable patients, 3 (7.5%) patients experienced a partial response (PR), 4 (10%) patients experienced prolonged stable disease (SD) for greater than or equal to 6 months and 12 (30%) patients experienced stable disease (SD) for less than 6 months. The median progression-free survival of the 40 evaluable patients was seen to be 1.9 months and the median overall survival was seen to be 8.7 months. We anticipate that additional results from this trial will be presented in the first half of 2017.

Safety Database . Our safety database includes over 3,000 patients who have been treated with neratinib. To date, the most significant grade 3 or higher adverse event associated with neratinib has been diarrhea, which occurs in approximately 30% of patients receiving the drug. Historically, once diarrhea occurred, patients were treated with loperamide and/or a reduction in the dose of neratinib. We have evaluated a prophylactic protocol pursuant to which a high dose of loperamide, approximately 16 mg, is given together with the initial dose of neratinib and then tapered down during the first cycle of treatment. We plan to continue evaluating this protocol as the preliminary data has suggested that this prophylactic regimen significantly reduces the incidence of diarrhea with neratinib.

In February 2015, Puma initiated a Phase II open-label trial of neratinib monotherapy for one year in 120 patients with early HER2-positive breast cancer who have completed one year of adjuvant t rastuzumab, or the CONTROL trial. This study population is analogous to the patient population from the ExteNET trial . The purpose of the Phase II trial is to investigate the effect of 2 cycles of high-dose loperamide on diarrhea incidence and severity. In the original protocol, 4 mg loperamide is self-administered with the first dose of neratinib, followed by 2 mg loperamide every 4 hours for the first 3 days, reducing to 2 mg loperamide every 6 to 8 hours through the first 2 cycles of therapy. With Ame ndment 1 of the protocol, the loperamide dosing schedule was modified to simplify the regimen. Following Amendment 1 of the protocol, 4 mg loperamide is self-administered with the first dose of neratinib, followed by 4 mg loperamide three times a day for 2 weeks, followed by 4 mg loperamide twice daily through the first 2 cycles of therapy. After two cycles, patients do not take loperamide prophylactically but take it as needed throughout the remainder of the treatment duration if diarrhea occurs.

In December 2016, interim results from the CONTROL trial were presented at the 2016 CTRC-AACR San Antonio Breast Cancer Symposium (SABCS). In the trial, patients with HER2-positive early-stage breast cancer who had completed trastuzumab-based adjuvant therapy received neratinib daily for a period of one year. High dose loperamide prophylaxis was given for the first 2 cycles (56 days) of treatment. Initially, the loperamide dosing used was 16 mg on day 1, then 12 mg on days 2 and 3 and then 6-8 mg on days 4-56 (original dosing). The protocol was later amended to simplify the regimen such that patients took 12 mg on days 1-14 and 8 mg on days 15-56 (modified dosing). The CONTROL trial has recently been expanded to include prophylaxis with the combination of loperamide and budesonide, a locally acting corticosteroid that we believe targets the inflammation identified in a preclinical model of neratinib-induced diarrhea.

The interim analysis of the trial presented in the poster included a total of 135 patients who received neratinib plus loperamide prophylaxis (28 patients taking the original dosing and 107 patients taking the modified dosing) and 40 patients who received neratinib plus loperamide prophylaxis for 2 cycles and budesonide for 1 cycle.

The results of the trial (data cut-off of November 2016) showed that the incidence of grade 3 diarrhea for the total 135 patients who received the loperamide prophylaxis was 28.1%. For the 28 patients who received loperamide using the original dosing regimen the grade 3 diarrhea rate was 25.0% and for the 107 patients who received the modified loperamide dosing regimen the grade 3 diarrhea rate was 29.0%. For the patients in the original dosing group, 71% of the patients who experienced grade 3 diarrhea were known to be non-compliant with the loperamide regimen and for the patients in the modified loperamide dosing regimen, 35% of the patients were known to be non-compliant with their loperamide dosing regimen. For the 135 patients who received the loperamide prophylaxis, the median number of grade 3 diarrhea episodes per patient was 1 and the median cumulative duration of grade 3 diarrhea was 3 days. For the 135 patients who received loperamide prophylaxis, 18.5% discontinued neratinib due to diarrhea.

For the 40 patients who received the combination of loperamide plus budesonide, the results of the trial (data cut-off of November 2016) showed that the incidence of grade 3 diarrhea was 15.0%. None of the patients who experienced grade 3 diarrhea were non-compliant with the lope ramide plus budesonide regimen. The median number of grade 3 diarrhea episodes per patient was 1 and the median cumulative duration of grade 3 diarrhea was 2.5 days. For the 40 patients who received loperamide plus budesonide prophylaxis, 5.0% discontinued neratinib due to diarrhea. Further information is provided in Table 1 below:

Table 1: Characteristics of Treatment-Emergent Diarrhea

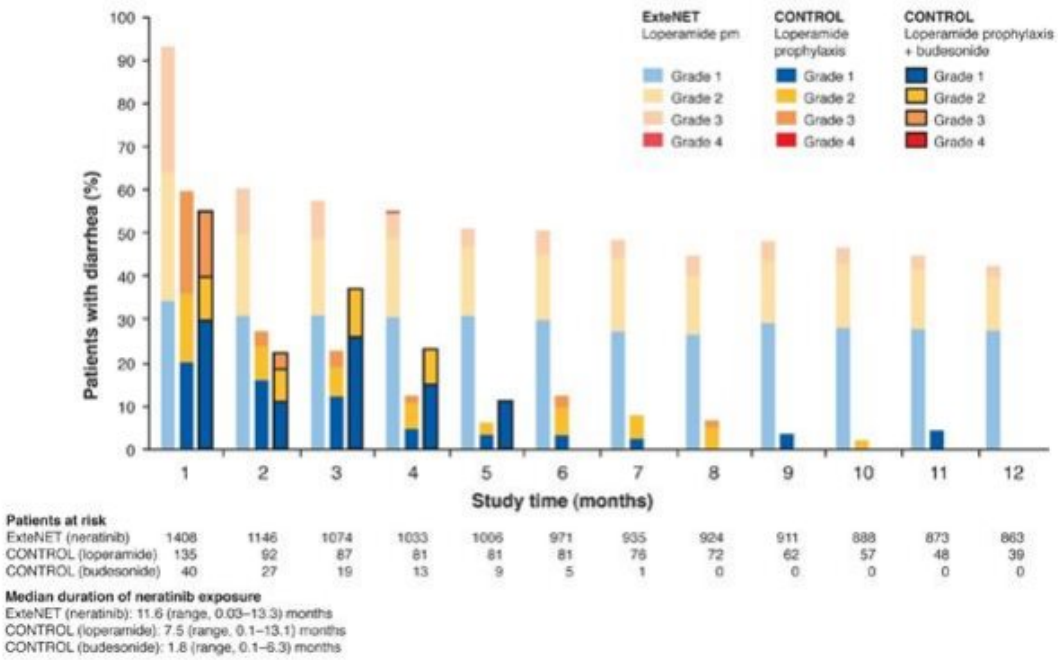
Study	**CONTROL**				**ExteNET**
	Loperamide cohort			**Budesonide cohort**	**Neratinib arm**
Prophylaxis **Prophylaxis**	**Original schedule (n=28)**	**Modified schedule (n=107)**	**Loperamide total (N=135)**	**Loperamide + budesonide (N=40)**	**Loperamide prn (N=1408)**
Diarrhea, %					
Any grade	82.1	73.8	75.6	65	95.4
Grade 1	35.7	21.5	24.4	32.5	22.9
Grade 2	21.4	23.4	23	17.5	32.5
Grade 3 [a]	25	29	28.1	15	39.8
Grade 4	0	0	0	0	0.1
Median cumulative duration, days					
Grade ≥2	5	4	4	3	10
Grade ≥3 [b]	2	3	3	2.5	5
Median diarrhea episodes/patient					
Any grade	2	2	2	2	8
Grade ≥2	2	1	2	1	3
Grade ≥3 [b]	1	1	1	1	2
Action taken, %					
Dose hold	7.1	12.1	11.1	7.5	33.9
Dose reduction	10.7	7.5	8.1	5	26.4
Discontinuation	28.6	15.9	18.5	5	16.8
Hospitalization	0	1.9	1.5	0	1.4
Duration of neratinib treatment, months					
Median	9.7	7.4	7.5	1.8	11.6
Range	0.1–13.1	0.1–12.8	0.1–13.1	0.1–6.3	0.03–13.3

[a] Non-compliance with loperamide prophylaxis in patients with grade 3 diarrhea was 71% with the original loperamide schedule, 35% with the modified loperamide schedule, and 100% with loperamide prophylaxis plus budesonide.

[b] No grade 4 events in the CONTROL study; one grade 4 event in the ExteNET study.

In the ExteNET trial, higher grade (grade 2 and grade 3) diarrhea occurred early and persisted throughout the duration of the 12-month treatment period. In the CONTROL trial, in both the loperamide prophylaxis and loperamide plus budesonide prophylaxis arm s, the results showed that higher grade diarrhea (grade 2 and 3) occurred early but did not typically recur. This is shown in more detail in Figure 1 below:

Figure 1: Treatment Emergent Diarrhea by Month in ExteNET versus CONTROL



The grade 3 diarrhea rates seen in the loperamide cohort have increased over what was previously reported in December 2015 (n=50, grade 3 diarrhea rate 16%). During the course of the CONTROL trial, there has been an increase in the proportion of patients previously treated with pertuzumab (mainly in the neoadjuvant setting). More specifically in the data reported in December 2015, 18% (9 of 50 patients) had previously received pertuzumab. In the current data set, 40% (54 of 135 patients) of the patients in the combined loperamide prophylaxis arms received prior pertuzumab and 55% (22 of 40 patients) received prior pertuzumab in the budesonide arm.

For the 54 patients in the loperamide prophylaxis cohort who received prior pertuzumab, the grade 3 diarrhea rate was 35.2% (Table 2). For the 81 patients who did not receive prior pertuzumab, the grade 3 diarrhea rate was 23.5%. For the 22 patients in the budesonide cohort who received prior pertuzumab, the grade 3 diarrhea rate was 13.6%. For the 18 patients in the budesonide cohort who did not receive prior pertuzumab, the grade 3 diarrhea rate was 16.7%. This analysis suggests that prior pertuzumab exposure may have led to a higher rate of grade 3 diarrhea in CONTROL that was not effectively managed by loperamide prophylaxis alone but was more effectively managed by loperamide plus budesonide.

Table 2: Incidence of Grade 3 Diarrhea in CONTROL by Prior Pertuzumab Treatment

		Loperamide Cohort			**Budesonide Cohort**	
		Yes (n = 54)	No (n = 81)		Yes (n = 22)	No (n = 18)
Grade 3 Diarrhea	35.2%	23.5%		13.6%	16.7%	

We anticipate reporting additional data from the CONTROL trial in the second quarter of 2017.

PB272 (neratinib (oral))—Other Potential Applications

Non-Small Cell Lung Cancer (NSCLC)

Approximately 2% to 4% of patients with NSCLC have a HER2 mutation in the kinase domain. This mutation is believed to narrow the ATP binding cleft, which results in increased tyrosine kinase activity. The mutation is also believed to result in increased PI3K activity and mTOR activation. Published data suggests that patients with HER2-mutated non-small cell lung cancer do not respond to platinum chemotherapy and do not respond to epidermal growth factor receptor inhibitors.

In September 2014, we reported initial data from the ongoing, open label Phase II clinical trial of PB272 (neratinib) for the treatment of patients with NSCLC with HER2 mutations as a late-breaking oral presentation at the European Society for Medical Oncology 2014 Congress. In the trial, patients with confirmed Stage IIIB or Stage IV NSCLC with documented somatic HER2 mutations were randomized to receive either oral neratinib monotherapy at a dose of 240 mg per day or the combination of oral neratinib (at a dose of 240 mg daily) with intravenous temsirolimus administered at a dose of 8 mg per week. In order to attempt to reduce the neratinib-related diarrhea, high-dose loperamide prophylaxis (Imodium) was given to all patients in both arms of the study beginning on day 1 of neratinib dosing. The data presented in the oral presentation involved a total of 27 patients who completed the first stage of the trial; 13 of these patients received neratinib monotherapy and 14 of these patients received the combination of neratinib plus temsirolimus. The results of the study showed that the combination of PB272 and temsirolimus had acceptable tolerability. Historically the most frequently seen adverse event associated with neratinib has been diarrhea. In the previous Phase I trial of neratinib plus temsirolimus (published in the *Journal of Clinical Oncology* in 2014) the diarrhea with neratinib was seen to be dose dependent and its incidence increased with increasing neratinib dosage. In that Phase I trial, grade 3 or higher diarrhea was seen in approximately 30% of the patients treated with doses of neratinib that were 200 mg or higher. In the Phase II study, all patients received high-dose loperamide in order to attempt to prevent or reduce the neratinib-related diarrhea. For the 13 patients enrolled in the neratinib monotherapy arm, 1 patient (8%) experienced grade 3 diarrhea, and for the 14 patients enrolled in the combination of neratinib plus temsirolimus arm, 2 patients (14%) experienced grade 3 diarrhea. There were no grade 4 diarrhea events seen in the trial. For the 3 patients in the study (1 in the monotherapy arm, 2 in the combination arm) who experienced grade 3 diarrhea, 2 of the 3 patients were not compliant with the loperamide prophylaxis regimen and were not taking loperamide at the onset of grade 3 diarrhea.

The efficacy results from the trial showed that for the 13 patients in the trial who received neratinib monotherapy, no patient experienced a partial response, 7 patients (54%) achieved stable disease and 4 patients (31%) achieved clinical benefit (defined as a partial response or stable disease for 12 or more weeks). For the 14 patients who received the combination of neratinib plus temsirolimus, 3 patients (21%) experienced a partial response, 11 patients (79%) experienced stable disease and 9 patients (64%) achieved clinical benefit. The median PFS of the neratinib monotherapy arm was 2.9 months and the median PFS of the arm that received neratinib plus temsirolimus was 4.0 months. Patients continue to be enrolled in the arm of the trial that is receiving the combination of neratinib plus temsirolimus.

HER2 Mutation-Positive Solid Tumors

Based on the results from the Cancer Genome Atlas Study, we estimate that between 2% and 11% of each solid tumor has a mutation in HER2. In the United States, this includes new diagnoses of an estimated 7,000 - 7,500 patients with bladder cancer; 4,000 - 4,500 patients with colorectal cancer; 1,500 - 2,000 patients with glioblastoma; 1,000 patients with melanoma; 4,000 - 5,000 patients with prostate cancer; 1,000 patients with stomach cancer; and 1,000 - 2,000 patients with uterine cancer.

Basket Trial for HER2 Mutation-Positive Solid Tumors. In October 2013, we announced that we had initiated a Phase II clinical trial of neratinib as a single agent in patients with solid tumors that have an activating HER2 mutation (SUMMIT basket trial). The Phase II basket trial is an open-label, multicenter, multinational study to evaluate the safety and efficacy of PB272 administered daily to patients who have solid tumors with activating HER2 mutations. The study initially included six cohorts (baskets) of patients, each of which will include one of the following cancers: (i) bladder/urinary tract cancer; (ii) colorectal cancer; (iii) endometrial cancer; (iv) gastric/esophageal cancer; (v) ovarian cancer; and (vi) all other solid tumors (including prostate, melanoma and pancreatic cancer). Each basket will initially consist of seven patients. If a certain predetermined objective response rate is seen in the initial cohort of seven patients, the basket will be expanded to include a larger number of patients.

In May 2014, we announced that we expanded the first cohort from the Phase II clinical trial of PB272 in pat ients with solid tumors who have an activating HER2 mutation (basket trial). The cohort that has been expanded includes patients with metastatic breast cancer that is not HER2 amplified or overexpressed (HER2 negative) and has a HER2 mutation. In April 201 5, we announced that we expanded the cohort from the Phase II clinical trial of PB272 in patients with metastatic NSCLC that is not HER2 amplified or overexpressed (HER2 negative) and has a HER2 mutation. In December 2015, we announced that we expanded the cohort that includes patients with metastatic biliary duct (bile duct) cancer that is not HER2 amplified or overexpressed (HER2 negative) and has a HER2 mutation. In January 2017, we announced that we expanded the fourth cohort that includes patients with metastatic cervical cancer and whose tumors have a HER2 mutation. The cervical cancer patients initially entered the study in the "other solid tumors with a HER2 mutation" cohort and, due to the preliminary activity seen in the trial, we expanded a separ ate cervical cancer cohort pursuant to the protocol for the trial. The expanded HER2-mutant cervical cancer cohort will now enroll a total of 18 patients. We expect to present the full results from the SUMMIT study including each of these expanded cohorts in 2017.

HER2-Mutated, Non-Amplified Breast Cancer

A HER2 mutation in patients with HER2-negative breast cancer was identified as part of a study performed by the Cancer Genome Atlas Network and published in Cancer Discovery in December 2012. We believe this mutation may occur in an estimated 2% of patients with breast cancer. Pre-clinical data from this publication demonstrated that neratinib was active in pre-clinical models of HER2-negative breast cancer that have this HER2 mutation and that neratinib has more anti-cancer activity than either trastuzumab or lapatinib in cells with this mutation. A Phase II trial of neratinib in HER2-negative breast cancer patients who have a HER2 mutation opened for enrollment in December 2012.

As stated above, in May 2014 we expanded the first cohort from the SUMMIT trial of PB272 in patients with solid tumors who have an activating HER2 mutation (basket trial). Interim results from this ongoing Phase II trial were presented at the 2015 CTRC-AACR San Antonio Breast Cancer Symposium in December 2015. In the cohort, patients with HER2-mutant metastatic breast cancer were enrolled and received 240 mg of neratinib daily. Patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea. For the 20 patients in the cohort presented, 20 patients (100%) had HER2-negative disease, 17 patients (85%) were hormone receptor positive (estrogen receptor or progesterone receptor positive), and patients had received a median of 4 prior regimens in the metastatic setting (range 0-11 prior regimens) before entering the trial.

The primary endpoint of the trial was objective response at week 8 assessed by anatomic or metabolic imaging. The interim efficacy results from the trial showed that for the 19 efficacy evaluable patients in the breast cancer cohort, 6 patients (32%) experienced a response at week 8. This included one patient with a complete response and five patients with partial responses. The secondary endpoints of the trial included duration of response, clinical benefit rate and progression-free survival (PFS). The results of the trial showed that 3 patients (16%) had a confirmed objective response, 8 patients (42%) demonstrated clinical benefit and the median progression-free survival was 4.0 months.

The presentation also discussed that a bidirectional cross-talk between hormone receptor and HER2 signaling pathways can lead to endocrine resistance due to activated HER2 signaling and ER-mediated tumor proliferation as a potential resistance mechanism to sustained HER2 inhibition. Preclinical xenograft data has demonstrated that the combination of an anti-estrogen with a HER2 inhibitor results in enhanced anti-tumor activity in preclinical models of estrogen receptor positive/HER2-positive breast tumors. Based on this, the SUMMIT study was amended to allow for the combination of neratinib plus fulvestrant in eligible postmenopausal hormone receptor positive breast cancer patients. For the 3 response-evaluable patients who have been enrolled and received the combination of neratinib plus fulvestrant, 3 (100%) of 3 patients have shown a response, including one patient with a complete response and two patients with partial responses. There have also been two patients enrolled on the combination of neratinib plus fulvestrant after progressing on neratinib monotherapy. One (50%) of these two patients has demonstrated a partial response.

The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. Patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea. For the 130 patients enrolled across all solid tumor cohorts in the SUMMIT study, 26 patients (20%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for the patients in the entire SUMMIT study was 2 days. 2 patients (2%) in the SUMMIT study have permanently discontinued neratinib due to diarrhea and 20 patients (15%) have temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided. For the breast cancer mutation cohort, 7 of 20 patients (35%) experienced grade 3 diarrhea. The median duration of grade 3 diarrhea was 1 day. No patient (0%) in the breast cancer cohort permanently discontinued neratinib due to diarrhea and 4 patients (20%) temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided.

In December 2016, updated int erim results from the ongoing Phase II clinical trial of neratinib given as monotherapy and in combination with the anticancer drug fulvestrant were presented at the 2016 CTRC-AACR San Antonio Breast Cancer Symposium (SABCS). In the study, patients with H ER2 mutant metastatic breast cancer were enrolled and received 240 mg of neratinib daily either as monotherapy or in combination with fulvestrant. All patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea. For the 25 patients in the group who received neratinib monotherapy, 23 patients (92%) had HER2-negative disease, 20 patients (76%) were hormone receptor positive (estrogen receptor or progesterone recepto r positive), and patients had received a median of 4 prior lines of therapy in the metastatic setting (range 0-8 prior regimens) before entering the trial. For the 17 patients in the trial who received neratinib plus fulvestrant, 15 patients (88%) had HER2 -negative disease, 17 patients (100%) were hormone receptor positive (estrogen receptor or progesterone receptor positive), and patients had received a median of 4 prior lines of therapy in the metastatic setting (range 1-7 prior regimens) before entering the trial.

The interim efficacy results from the trial showed that for the 24 efficacy evaluable patients in the neratinib monotherapy cohort, 8 patients (33.3%) experienced an objective response, which included 3 patients with a complete response and 5 patients with partial responses. At week 8, 8 patients (33.3%) achieved an objective response, with 2 patients achieving a complete response and 6 patients achieving a partial response The secondary endpoints of the trial included confirmed objective response (complete response or partial response), clinical benefit rate and PFS. The results of the trial showed that 6 patients (25%) had a confirmed objective response, 10 patients (41.7%) demonstrated clinical benefit and the median PFS was 3.5 months.

For the 12 efficacy evaluable patients in the neratinib plus fulvestrant cohort, 7 patients (58.3%) experienced an objective response, which included 2 patients with a complete response and 5 patients with partial responses. At week 8, 5 patients (41.7%) achieved an objective response, with 2 patients achieving a complete response and 3 patients achieving a partial response. The secondary endpoints of the trial included confirmed objective response (complete response or partial response), clinical benefit rate and PFS. The results of the trial showed that 3 patients (25%) had a confirmed objective response, 7 patients (58.3%) demonstrated clinical benefit and the median progression free survival was 3.7 months. The progression free survival data may not be mature in the neratinib plus fulvestrant cohort as 4 of the 12 efficacy evaluable patients are continuing to receive study treatment without disease progression and an additional 5 patients have not yet had an assessment for efficacy.

The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. For the 25 patients enrolled in the neratinib monotherapy arm, 6 patients (24%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for the patients in the neratinib monotherapy cohort was 1 day. No patient in the neratinib monotherapy cohort has permanently discontinued neratinib due to diarrhea and 5 patients (20%) have temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided. For the 17 patients enrolled in the neratinib plus fulvestrant cohort, 2 of 17 patients (12%) experienced grade 3 diarrhea. The median duration of grade 3 diarrhea was 1 day and typically occurred during the first cycle of treatment. No patient (0%) in the neratinib plus fulvestrant cohort permanently discontinued neratinib due to diarrhea and 2 patients (12%) temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided.

In June 2016, we announced that positive results from a separate investigator sponsored Phase II trial of neratinib with HER2-mutated, non-amplified breast cancer were presented in a poster discussion session at the American Society of Clinical Oncology (ASCO) 2016 Annual Meeting.

In the trial, patients with HER2 mutated breast cancer (either in their primary or metastatic tumor) received 240 mg of neratinib daily. Patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea. For the 16 patients enrolled in the trial, 16 patients (100%) had HER2-negative disease, 15 patients (94%) were hormone receptor positive (estrogen receptor or progesterone receptor positive), and for the patients with metastatic disease, patients had received a median of 3 prior regimens (range 2-10 prior regimens) before entering the trial. Among these 16 patients, 14 had activating HER2 mutations and 2 patients had HER2 mutations of unknown significance.

The primary endpoint of the Phase II trial was clinical benefit rate, or CBR, defined as complete response, or CR, partial response, or PR, or stable disease, or SD, greater than or equal to six months. The trial was designed to detect a CBR of 20%. In the 14 patients with activating HER2 mutations, 5 (36%) achieved clinical benefit, including 1 patient (7%) with a CR, 1 patient (7%) with a PR, and 3 patients (21%) with SD for greater than or equal to six months. The median duration of response in these 5 patients was 6 (range 6-14+) months. The median progression-free survival for all 14 patients with activating HER2 mutations in the trial was 5.0 months. In the 2 patients with HER2 mutations of unknown significance, there was no clinical benefit seen with neratinib.

Based on the preclinical data described above that has demonstrated that the combination of an anti-estrogen with a HER2 inhibitor results in enhanced anti-tumor activity in preclinical models of estrogen receptor positive/HER2-mutated breast tumors, the study has been amended to administer the combination of neratinib plus fulvestrant in eligible hormone receptor positive breast cancer patients who have an activating HER2 mutation in the tumor. Enrollment in this cohort is currently ongoing and results from this cohort receiving the combination of fulvestrant plus neratinib is expected to be presented at a future medical meeting.

The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. For the 16 patients enrolled in the study, 4 patients (25%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for the patients in the study was 1.5 days.

We anticipate that additional data from this trial will be presented in 2017.

PB272 (neratinib (intravenous))

We also plan to develop neratinib as an intravenously administered agent. The intravenous version of neratinib resulted in higher exposure levels of neratinib in pre-clinical models. We believe this may result in higher blood levels of neratinib in patients, and may translate into enhanced efficacy. We are evaluating the intravenous formulation of neratinib and considering options relative to its development.

PB357

PB357 is an orally administered agent that is an irreversible TKI that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. PB357 is structurally similar to PB272. Pfizer completed single-dose Phase I trials of PB357. We are evaluating PB357 and considering options relative to its development.

Clinical Testing of Our Products in Development

Each of our products in development, and likely all future drug candidates we in-license, will require extensive pre-clinical and clinical testing to determine the safety and efficacy of the product applications prior to seeking and obtaining regulatory approval. This process is expensive and time consuming. In completing these trials, we are dependent upon third-party consultants, consisting mainly of investigators and collaborators, who will conduct such trials.

We and our third-party consultants conduct pre-clinical testing in accordance with Good Laboratory Practices, or GLP, and clinical testing in accordance with Good Clinical Practice standards, or GCP, which are international ethical and scientific quality standards utilized for pre-clinical and clinical testing, respectively. GCP is the standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials and the FDA requires compliance with GCP regulations in the conduct of clinical trials. Additionally, our pre-clinical and clinical testing completed in the EU is conducted in accordance with applicable EU standards, such as the EU Clinical Trials Directive (Directive 2001/20/EC of April 4, 2001), or the EU Clinical Trials Directive, and the national laws of the member states of the EU implementing its provisions.

We have entered into, and may enter into in the future, master service agreements with clinical research organizations, or CROs, with respect to initiating, managing and conducting the clinical trials of our products. These contracts contain standard terms for the type of services provided that contain cancellation clauses requiring between 30 and 45 days written notice and that obligate us to pay for any services previously rendered with prepaid, unused funds being returned to us.

Competition

The development and commercialization of new products to treat cancer is highly competitive and we expect considerable competition from major pharmaceutical, biotechnology and specialty cancer companies. As a result, there are and will likely continue to be extensive research and substantial financial resources invested in the discovery and development of new cancer products. Our potential competitors include, but are not limited to, Genentech, Novartis, Roche, Boehringer Ingelheim, Takeda, Array Biopharma and Ambit Biosciences. We are an early stage company with a limited history of operations and no experience with sales, marketing or commercial manufacturing. Many of our competitors have substantially more financial and technical resources than we do. In addition, many of our competitors have more experience than we have in pre-clinical and clinical development, manufacturing, regulatory and global commercialization. We are also competing with academic institutions, governmental agencies and private organizations that are conducting research in the field of cancer. We anticipate that we will face intense competition.

We expect that our products under development and in clinical trials will address major markets within the cancer sector. Our competition will be determined in part by the potential indications for which drugs are developed and ultimately approved by regulatory authorities. Additionally, the timing of market introduction of some of our potential products or of competitors' products may be an important competitive factor. Accordingly, the speed with which we can develop products, complete pre-clinical testing, clinical trials and approval processes, and supply commercial quantities to market are expected to be important competitive factors. We expect that competition among products approved for sale will be based on various factors, including product efficacy, safety, reliability, availability, price, reimbursement and patent position.

Sales and Marketing

We currently have no sales, marketing or distribution capabilities and only a limited number of our employees have experience in marketing or selling pharmaceutical products. To achieve commercial success for any of our proposed products, if approved, we must either develop a direct sales, marketing and distribution organization or enter into arrangements with third parties to market, sell and distribute such products. In June and July 2016, we submitted an MAA, to the European Medicines Agency, or the EMA, and filed a New Drug Application, or NDA, with the FDA respectively, for neratinib for the extended adjuvant treatment of patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy. We are continuing to evaluate potential commercialization options for the extended adjuvant setting, including developing a direct sales force, contracting with third parties to provide sales and marketing support, some combination of these two options or other strategic options.

Intellectual Property and License Agreements

We hold a worldwide exclusive license under our license agreement with Pfizer to four granted U.S. patents and nine pending U.S. patent applications, as well as foreign counterparts thereof, and other patent applications and patents claiming priority therefrom.

In the United States, we have a license to an issued patent, which currently will expire in 2025, for the composition of matter of neratinib, our lead compound. We have a license to an issued U.S. patent covering a family of compounds including neratinib, as well as equivalent patents in the EU and Japan, that currently expire in 2019. We also have a license to an issued U.S. patent for the use of neratinib in the treatment of breast cancer, which currently expires in 2025, and an issued U.S. polymorph patent for neratinib, which currently expires in 2028. In jurisdictions which permit such, we will seek patent term extensions where possible for certain of our patents. We plan to pursue additional patents in and outside the United States covering additional therapeutic uses and polymorphs of neratinib from these existing applications. In addition, we will pursue patent protection for any new discoveries or inventions made in the course of our development of neratinib.

If we obtain marketing approval for neratinib or other drug candidates in the United States or in certain jurisdictions outside the United States, we may be eligible for regulatory protection, such as five years of new chemical entity exclusivity and, as mentioned above, up to five years of patent term extension potentially available in the United States under the Hatch-Waxman Act. In addition, eight to 11 years of data and marketing exclusivity potentially are available for new drugs in the European Union; up to five years of patent extension are potentially available in Europe (Supplemental Protection Certificate), and eight years of data exclusivity are potentially available in Japan. There can be no assurance that we will qualify for any such regulatory exclusivity, or that any such exclusivity will prevent competitors from seeking approval solely on the basis of their own studies. See “Government Regulation” below.

The intellectual property portfolio that was licensed from Pfizer in 2011 when we licensed neratinib included issued patents in a number of countries, including in Europe (EP 1848414), as well as pending patent applications in several countries, including the United States, relating to methods of treating gefitinib- and/or erlotinib-resistant cancer by administering an irreversible epidermal growth factor receptor inhibitor. More specifically, the patent that was issued in Europe in April 2011 included specific claims that included a pharmaceutical composition for use in treating cancer in a subject with a cancer having a mutation in epidermal growth factor receptor with a T790M mutation. On November 28, 2011, Boehringer Ingelheim International GmbH filed an opposition to this patent asking for this patent to be revoked. The Oral Proceedings of the European Patent Office were held in Munich, Germany on February 4, 2014. The decision of the European Patent Office was to uphold the granted claims of the European patent that relate to the T790M mutation without any modification. This included specific claims that include claims for the pharmaceutical composition comprising an irreversible epidermal growth factor receptor inhibitor for use in treating cancer in a subject having a T790M mutation, and claims for the pharmaceutical composition for use in the treatment of numerous cancers, including lung cancer and non-small cell lung cancer. In September 2015, we were advised of the issuance by the United States Patent and Trademark Office of a Notice of Allowance for U.S. Patent Application 11/883,474 titled “Method for Treating Gefitinib Resistant Cancer.”

Our goal is to obtain, maintain and enforce patent protection for our products, formulations, processes, methods and other proprietary technologies, preserve our trade secrets, and operate without infringing on the proprietary rights of other parties, both in the United States and in other countries. Our policy is to actively seek to obtain, where appropriate, the broadest intellectual property protection possible for our current product candidates and any future product candidates, proprietary information and proprietary technology through a combination of contractual arrangements and patents, both in the United States and abroad. However, even patent protection may not always provide us with complete protection against competitors who seek to circumvent our patents. See “Risk Factors—Risks Related to Our Intellectual Property—Our proprietary rights may not adequately protect our intellectual property and potential products, and if we cannot obtain adequate protection of our intellectual property and potential products, we may not be able to successfully market our potential products.”

We depend upon the skills, knowledge and experience of our scientific and technical personnel, as well as that of our advisors, consultants and other contractors, none of which is patentab le. To help protect our proprietary know-how, which is not patentable, and inventions for which patents may be difficult to obtain or enforce, we rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we requi re all of our employees, consultants, advisors and other contractors to enter into confidentiality agreements that prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments , discoveries and inventions important to our business.

License Agreements

In August 2011, Former Puma entered into an agreement pursuant to which Pfizer agreed to grant to Former Puma a worldwide license for the development, manufacture and commercialization of neratinib (oral), neratinib (intravenous), PB357, and certain related compounds. Pursuant to the terms of the agreement, the license would not become effective until Former Puma closed a capital raising transaction in which it raised at least $25 million in aggregate net proceeds and had a net worth of at least $22.5 million. Upon the closing of the financing that preceded the Merger, this condition was satisfied.

We assumed the license agreement, in accordance with its terms, in the Merger. The license is exclusive with respect to certain patent rights owned or licensed by Pfizer, or the Licensor. Under the license agreement, the Licensor is obligated to transfer to us certain information, records, regulatory filings, materials and inventory controlled by the Licensor and relating to or useful for developing these compounds and to continue to conduct certain ongoing clinical studies until a certain time. After that time, we are obligated to continue such studies pursuant to an approved development plan, including after the license agreement terminates for reasons unrelated to the Licensor's breach of the license agreement, subject to certain specified exceptions. We are also obligated to commence a new clinical trial for a product containing one of these compounds within a specified period of time and use commercially reasonable efforts to complete such trial and achieve certain milestones as provided in a development plan. If certain of our out-of-pocket costs in completing such studies exceed a mutually agreed amount, the Licensor will pay for certain additional out-of-pocket costs to complete such studies. We must use commercially reasonable efforts to develop and commercialize products containing these compounds in specified major-market countries and other countries in which we believe it is commercially reasonable to develop and commercialize such products.

As consideration for the license, we are required to make payments totaling $187.5 million upon the achievement of certain milestones if all such milestones are achieved. In addition, the license agreement originally stipulated that should we commercialize any of the compounds licensed from the Licensor or any products containing any of these compounds, we will be obligated to pay to the Licensor incremental annual royalties between approximately 10% and 20% of net sales of all such products, subject, in some circumstances, to certain reductions.

In July 2014, the Company signed an amendment to the license agreement with the Licensor. The amendment to the license agreement provides that the Company would be solely responsible for the expenses incurred or accrued in conducting the ongoing legacy clinical trials after December 31, 2013. These costs were previously the responsibility of the Licensor.

In addition, under the amended agreement, annual royalties to be paid on net sales of licensed products were reduced from a tiered royalty rate structure ranging between 10% to 20% to a fixed rate in the low to mid-teens. The Licensor and the Company have agreed to continue to cooperate to effect the transfer to the Company of certain records, regulatory filings, materials and inventory controlled by the Licensor as promptly as reasonably practicable.

Our royalty obligation continues, on a product-by-product and country-by-country basis, until the later of (i) the last to expire valid claim of a licensed patent covering the applicable licensed product in such country, or (ii) the earlier of generic competition for such licensed product reaching a certain level of sales in such country or expiration of a certain time period after first commercial sale of such licensed product in such country. In the event that we sublicense the rights granted to us under the license agreement with the Licensor to a third party, the same milestone and royalty payments are required. We can terminate the license agreement at will at any time after April 4, 2013, or for safety concerns, in each case upon specified advance notice. Each party may terminate the license agreement if the other party fails to cure any breach of a material obligation by such other party within a specified time period. The Licensor may terminate the license agreement in the event of our bankruptcy, receivership, insolvency or similar proceeding. The license agreement contains other customary clauses and terms as are common in similar agreements in the industry.

Government Regulation

United States—FDA Process

The research, development, testing, manufacture, labeling, promotion, advertising, distribution and marketing, among other things, of drug products are extensively regulated by governmental authorities in the United States and other countries. In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and its implementing regulations. Failure to comply with the applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, warning letters, fines, civil penalties, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or criminal prosecution.

Drug Approval Process . None of our drug product candidates may be marketed in the United States until the drug has received FDA approval. The steps required before a drug may be marketed in the United States generally include the following:

- completion of extensive pre-clinical laboratory tests, animal studies, and formulation studies in accordance with the FDA's GLP regulations;
- submission to the FDA of an Investigational New Drug, or IND, application for human clinical testing, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials in accordance with GCP requirements to establish the safety and efficacy of the drug for each proposed indication;
- submission to the FDA of an NDA after completion of all pivotal clinical trials;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the active pharmaceutical ingredient, or API, and finished drug product are produced and tested to assess compliance with current Good Manufacturing Practices, or cGMPs; and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Pre-clinical tests include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies. The conduct of the pre-clinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the pre-clinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the conduct of the trial, such as whether human research subjects will be exposed to an unreasonable health risk. In such a case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. We cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin.

Clinical trials involve administration of the investigational drug to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol must be provided to the FDA as part of a separate submission to the IND. Further, an Institutional Review Board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the study protocol and informed consent information for study subjects for any clinical trial before it commences at that center, and the IRB must monitor the study until it is completed. There are also requirements governing reporting of ongoing clinical trials and clinical trial results to public registries. Study subjects must sign an informed consent form before participating in a clinical trial. Clinical trials necessary for product approval typically are conducted in three sequential phases, but the phases may overlap. Phase I usually involves the initial introduction of the investigational drug into a limited population, typically healthy humans, to evaluate its short-term safety, dosage tolerance, metabolism, pharmacokinetics and pharmacologic actions, and, if possible, to gain an early indication of its effectiveness. Phase II usually involves trials in a limited patient population to (i) evaluate dosage tolerance and appropriate dosage; (ii) identify possible adverse effects and safety risks; and (iii) evaluate preliminarily the efficacy of the drug for specific targeted indications. Multiple Phase II clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase III clinical trials. Phase III trials, commonly referred to as pivotal studies, are undertaken in an expanded patient population at multiple, geographically dispersed clinical trial centers to further evaluate clinical efficacy and test further for safety by using the drug in its final form. There can be no assurance that Phase I, Phase II or Phase III testing will be completed successfully within any specified period of time, if at all. Furthermore, we, the FDA or an IRB may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Moreover, the FDA may approve an NDA for a product candidate, but require that the sponsor conduct additional clinical trials to further assess the drug after NDA approval under a post-approval commitment. Post-approval trials are typically referred to as Phase IV clinical trials.

During the development of a new drug, sponsors are given an opportunity to meet with the FDA at certain points. These points may be prior to submiss ion of an IND, at the end of Phase II, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and the FDA to reach an agreement on the next phase of development. Sponsors typically use the end of Phase II meeting to discuss their Phase II clinical results and present their plans for the pivotal Phase III clinical trial that they believe will support approval of the new drug. A sponsor may request an SPA to reach an agreement with the FDA that the protocol design, clinical endpoints, and statistical analyses are acceptable to support regulatory approval of the product candidate wi th respect to effectiveness in the indication studied. If such an agreement is reached, it will be documented and made part of the administrative record, and it will be binding on the FDA except in limited circumstances, such as if the FDA identifies a sub stantial scientific issue essential to determining the safety or effectiveness of the product after clinical studies begin, or if the sponsor fails to follow the protocol that was agreed upon with the FDA. There is no guarantee that a study will ultimately be adequate to support an approval, even if the study is subject to an SPA.

Concurrent with clinical trials, companies usually complete additional animal safety studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and the manufacturer must develop methods for testing the quality, purity and potency of the final drugs. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Assuming successful completion of the required clinical testing, the results of pre-clinical studies and of clinical trials, together with other detailed information, including information on the manufacture and composition of the drug, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. An NDA must be accompanied by a significant user fee, which is waived for the first NDA submitted by a qualifying small business. In July 2012, the Food and Drug Administration Safety and Innovation Act, or FDASIA, was signed into law. Among other things, FDASIA reauthorizes the FDA's authority to collect user fees from industry participants to fund reviews of innovator drugs.

The testing and approval process requires substantial time, effort and financial resources. The FDA will review the NDA and may deem it to be inadequate to support approval, and we cannot be sure that any approval will be granted on a timely basis, if at all. The FDA may also refer the application to the appropriate advisory committee, typically a panel of clinicians, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of the advisory committee, but it typically follows such recommendations.

Before approving an NDA, the FDA inspects the facility or the facilities at which the drug and/or its active pharmaceutical ingredient is manufactured and will not approve the product unless the manufacturing is in compliance with cGMPs. If the FDA evaluates the NDA and the manufacturing facilities are deemed acceptable, the FDA may issue an approval letter, or in some cases a Complete Response Letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of NDA approval, the FDA may require post-marketing testing and surveillance to monitor the drug's safety or efficacy, or impose other conditions. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or additional pivotal Phase III clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data from clinical trials is not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Alternatively, the FDA could also approve the NDA with a Risk Evaluation and Mitigation Strategy to mitigate risks of the drug, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. Once the FDA approves a drug, the FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing, including Phase IV clinical trials, and surveillance programs to monitor the safety effects of approved products that have been commercialized. The FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs or other information.

Expedited Review and Approval . The FDA has various programs, including fast track designation, priority review, accelerated approval, and breakthrough therapy designation, which are intended to expedite or simplify the process for reviewing drugs and/or provide for approval on the basis of surrogate endpoints. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened. Generally, drugs that may be eligible for these programs are those for serious or life-threatening diseases or conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, fast track designation is designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases or conditions and which demonstrate the potential to address an unmet medical need. Priority review is designed to give drugs for serious conditions that offer significant improvement in safety or effectiveness an initial review within six months as

compared to a standard review time of 10 months. Although fast track designation and priority review do not affect the standards for approval, the FDA will attem pt to facilitate early and frequent meetings with a sponsor of a fast track designated drug and expedite review of the application for a drug designated for priority review. The FDA may also initiate review of sections of an NDA before the application is c omplete for drugs with fast track designation. This "rolling review" is available if the applicant provides and the FDA approves a schedule for submission of portions of the application. Drugs for serious conditions are also eligible for accelerated approv al, which provides an earlier approval of drugs, including fast track products, upon a determination that the product has an effect on a surrogate endpoint, which is a laboratory measurement or physical sign used as an indirect or substitute measurement re presenting a clinically meaningful outcome, or an effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinica l benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform post- marketing clinical trials. Finally, breakthrough therapy designation, which was enacted in FDASIA, is for drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clin ical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakth rough therapies receive all the benefits of a fast track designation, as well as intensive guidance on efficient drug development and organizational commitment involving senior managers in the FDA. In June 2013, the FDA issued draft guidance on these exped ited review and approval programs, providing the first available guidance for industry regarding the FDA's implementation of the breakthrough therapy designation framework, and in May 2014, the FDA issued final guidance. We may seek to utilize one or more of these expedited programs for our product candidates in the future, but even if we were to obtain fast track designation, priority review, accelerated approval and/or breakthrough therapy designation, there is no guarantee that it would result in a quick er review or approval of our products, if any.

Post-Approval Requirements . After a drug has been approved by the FDA for sale, the FDA may require that certain post-approval requirements be satisfied, including the conduct of additional clinical studies. In addition, certain changes to an approved product, such as adding new indications, making certain manufacturing changes, or making certain additional labeling claims, are subject to further FDA review and approval. Before a company can market products for additional indications, it must obtain additional approvals from the FDA. Obtaining approval for a new indication generally requires that additional clinical studies be conducted. A company cannot be sure that any additional approval for new indications for any product candidate will be approved on a timely basis, or at all.

If post-approval conditions are not satisfied, the FDA may withdraw its approval of the drug. In addition, holders of an approved NDA are required to (i) report certain adverse reactions to the FDA and maintain pharmacovigilance programs to proactively look for these adverse events; (ii) comply with certain requirements concerning advertising and promotional labeling for their products; and (iii) continue to have quality control and manufacturing procedures conform to cGMPs after approval. The FDA periodically inspects the sponsor's records related to safety reporting and/or manufacturing facilities; this latter effort includes assessment of ongoing compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. We intend to use third-party manufacturers to produce our products in clinical and commercial quantities, and future FDA inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

Patent Term Restoration and Marketing Exclusivity . Depending upon the timing, duration and specifics of FDA approval of the use of our drugs, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the extension must be requested prior to expiration of the patent. The U.S. Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Data and market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent data exclusivity within the Uni ted States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible fo r the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or an NDA submitted under section 505(b)(2) of the FDCA by another company for another version of such drug w here the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provi des three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, conducted or sponsored by the applicant are deemed by the FDA to be essential to the app roval of the application, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct, or obtain a right of r eference to all of the pre-clinical studies, adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials and approval of foreign countries or economic areas, such as the EU, before we may market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

In the European Economic Area, or EEA, which is comprised of the 28 member states of the EU, or Member States, plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MAs:

- Community MAs – These are issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the EMA, and are valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA; for products that constitute a significant therapeutic, scientific or technical innovation; or for products that are in the interest of public health in the EU.
- National MAs – These are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, and are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure, an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State. The competent authority of the Reference Member State prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling or packaging proposed by the Reference Member State, the product is subsequently granted a National MA in all the Member States, i.e., in the Reference Member State and the Member States Concerned.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA assess the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

As in the United States, it may be possible in foreign countries to obtain a period of market and/or data exclusivity that would have the effect of postponing the entry into the marketplace of a competitor’s generic product. For example, if any of our products receive marketing approval in the EEA, we expect they will benefit from eight years of data exclusivity and 10 years of marketing exclusivity. An additional non-cumulative one-year period of marketing exclusivity is possible if during the data exclusivity period (the first eight years of the 10-year marketing exclusivity period), we obtain an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies. The data exclusivity period begins on the date of the product’s first marketing authorization in the EEA and prevents generics from relying on the marketing authorization

holder's pharmacological, toxicological and clinical data for a period of eight years. After eight years, a generic product application may be submitted and generic companies may rely on the marketing authorization holder's data. However, a generic cannot launch until two years later (or a total of 10 years after the first marketing authorization in the EU of the innovator product), or three years later (or a total of 11 years after the first marketing authorization in the EU of t he innovator product) if the marketing authorization holder obtains marketing authorization for a new indication with significant clinical benefit within the eight-year data exclusivity period. In Japan, our products may be eligible for eight years of data exclusivity. There can be no assurance that we will qualify for such regulatory exclusivity, or that such exclusivity will prevent competitors from seeking approval solely on the basis of their own studies.

When conducting clinical trials in the EU, we must adhere to the provisions of the European Union Clinical Trials Directive and the laws and regulations of the EU Member States implementing them. These provisions require, among other things, that the prior authorization of an Ethics Committee and the competent Member State authority is obtained before commencing the clinical trial.

Coverage and Reimbursement

In the United States and internationally, sales of products that we market in the future, and our ability to generate revenues on such sales, are dependent, in significant part, on the availability of adequate coverage and reimbursement from third-party payors, such as state and federal governments, managed care providers and private insurance plans. Private insurers, such as health maintenance organizations and managed care providers, have implemented cost-cutting and reimbursement initiatives and likely will continue to do so in the future. These include establishing formularies that govern the drugs and biologics that will be offered and the out-of-pocket obligations of member patients for such products. We may need to conduct pharmacoeconomic studies to demonstrate the cost-effectiveness of our products for formulary coverage and reimbursement. Even with such studies, our products may be considered less safe, less effective or less cost-effective than existing products, and third-party payors may not provide coverage and reimbursement for our product candidates, in whole or in part.

In addition, particularly in the United States and increasingly in other countries, we are required to provide discounts and pay rebates to state and federal governments and agencies in connection with purchases of our products that are reimbursed by such entities. It is possible that future legislation in the United States and other jurisdictions could be enacted to potentially impact reimbursement rates for the products we are developing and may develop in the future and could further impact the levels of discounts and rebates paid to federal and state government entities. Any legislation that impacts these areas could impact, in a significant way, our ability to generate revenues from sales of products that, if successfully developed, we bring to market.

Political, economic and regulatory influences are subjecting the healthcare industry in the United States to fundamental changes. There have been, and we expect there will continue to be, legislative and regulatory proposals to change the healthcare system in ways that could significantly affect our future business. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, enacted in March 2010, substantially changes the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, ACA establishes:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents;
- a new Medicare Part D coverage gap discount program, in which pharmaceutical manufacturers who wish to have their drugs covered under Part D must offer discounts to eligible beneficiaries during their coverage gap period, or the donut hole; and
- a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program.

We expect that the new presidential administration and U.S. Congress will seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. Since taking office, President Trump has continued to support the repeal of all or portions of the ACA. In January 2017, the House and Senate passed a budget resolution that authorizes congressional committees to draft legislation to repeal all or portions of the ACA and permits such legislation to pass with a majority vote in the Senate. President Trump has also recently issued an executive order in which he stated that it is his administration's policy to seek the prompt repeal of the ACA and directed executive departments and federal agencies to waive, defer, grant exemptions from, or delay the implementation of the provisions of the ACA to the maximum extent permitted by law. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by ACA.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government

programs. This includes aggregate reductions to Medicare payments to p roviders of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2025 unless additional Congressional action is taken. On January 2, 2013, President Obama si gned into law the American Taxpayer Relief Act of 2012, or the ATRA, which among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted i n several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodo logies for drug products. For example, the 21st Century Cures Act changes the reimbursement methodology for infusion drugs and biologics furnished through durable medical equipment in an attempt to remedy over- and underpayment of certain drugs.

In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system. Future legislation, or regulatory actions implementing recent or future legislation may have a significant effect on our business. Our ability to successfully commercialize products depends in part on the extent to which reimbursement for the costs of our products and related treatments will be available in the United States and worldwide from government health administration authorities, private health insurers and other organizations. The adoption of certain proposals could limit the prices we are able to charge for our products, the amounts of reimbursement available for our products, and limit the acceptance and availability of our products. Therefore, substantial uncertainty exists as to the reimbursement status of newly approved health care products by third-party payors.

Sales and Marketing

The FDA regulates all advertising and promotion activities for products under its jurisdiction prior to and after approval, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental NDA, which may require us to collect additional data or conduct additional pre-clinical studies and clinical trials. Failure to comply with applicable FDA requirements may subject a company to adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA.

Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties, and often reflect a physician's belief that the off-label use is the best treatment for the patient. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. Failure to comply with applicable FDA requirements may subject a company to adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA.

Outside the United States, our ability to market a product is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country.

Manufacturing

We do not currently have our own manufacturing facilities. We intend to continue to use our financial resources to accelerate development of our drug candidates rather than diverting resources to establish our own manufacturing facilities. We intend to meet our pre-clinical and clinical trial manufacturing requirements by establishing relationships with third-party manufacturers and other service providers to perform these services for us. While our drug candidates were being developed by Pfizer, both the drug substance and drug product were manufactured by third-party contractors. We are currently using the same third-party contractors to manufacture, supply, store and distribute drug supplies for our clinical trials. We believe that we have manufactured sufficient quantities of the drug to support at least the first year of launch in the extended adjuvant breast cancer indication and plan to continue to manufacture the drug in 2017 to further support the commercial launch of the drug.

Should any of our drug candidates obtain marketing approval, we anticipate establishing relationships with third-party manufacturers and other service providers in connection with commercial production of our products. We have some flexibility in securing other manufacturers to produce our drug candidates; however, our alternatives may be limited due to proprietary technologies or methods used in the manufacture of some of our drug candidates.

Other Healthcare Laws

We may also be subject to various federal and state laws pertaining to health care "fraud and abuse," including anti-kickback laws and false claims laws, data privacy and security laws and transparency laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented, for payment to third-party payors (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. In addition, some state prohibitions apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs. Our activities relating to the sale and marketing of our products may be subject to scrutiny under any of these laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal health care programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also may be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called "responsible corporate officer" doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing. Given the penalties that may be imposed on companies and individuals if convicted, allegations of such violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or determine that we or our executive officers had violated these laws, our business could be harmed. In addition, private individuals have the ability to bring similar actions.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

Further, there are new federal requirements under ACA and an increasing number of state laws that require manufacturers to disclose and make reports to the government of pricing and marketing information as well as any "transfer of value" made or distributed to physicians, teaching hospitals and other healthcare providers. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our future reporting actions could be subject to the penalty provisions of the applicable state and/or federal authorities.

Our activities could be subject to challenge for the reasons discussed above due to the breadth of these laws and the increasing attention being given to them by law enforcement authorities. The costs of defending such claims, as well as any sanctions imposed or negative public perceptions resulting therefrom, could require us to restructure our operations and have a material adverse effect on our financial performance.

Similar rigid restrictions are imposed on the promotion and marketing of medicinal products in the EU and other countries. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we may not be directly responsible for the promotion and marketing of our drug candidates, if approved, any inappropriate activity by international distribution partners could have adverse implications for us.

Other Laws an d Regulatory Processes

We are subject to a variety of financial disclosure and securities trading regulations as a public company in the United States with securities traded on the NASDAQ Global Select Market, including laws relating to the oversight activities of the Securities and Exchange Commission, or the SEC, and the rules and regulations of The NASDAQ Stock Market LLC. In addition, the Financial Accounting Standards Board, or FASB, the SEC, and other bodies that have jurisdiction over the form and content of our accounts, our financial statements and other public disclosure are constantly discussing and interpreting proposals and existing pronouncements designed to ensure that companies best display relevant and transparent information relating to their respective businesses.

Our present and future business has been and will continue to be subject to various other laws and regulations. Various laws, regulations and recommendations relating to safe working conditions, laboratory practices, experimental use of animals, and the purchase, storage, movement, import and export, and use and disposal of hazardous or potentially hazardous substances used in connection with our research work are or may be applicable to our activities. Certain agreements entered into by us involving exclusive license rights or acquisitions may be subject to national or supranational antitrust regulatory control, the effect of which cannot be predicted. The extent of government regulation that might result from future legislation or administrative action cannot accurately be predicted.

Research and Development Expenses

Research and development activities, which include personnel costs, research supplies, clinical and pre-clinical study costs, are the primary source of our overall expenses. Such expenses related to the research and development of our product candidates totaled $222.8 million for the year ended December 31, 2016, $208.5 million for the year ended December 31, 2015 and $122.9 million for the year ended December 31, 2014.

Employees

As of December 31, 2016, we had 160 employees, all of whom are full-time employees. We believe our relations with our employees are good. Over the course of the next year, we anticipate hiring up to 13 additional full-time employees devoted to clinical activities, 17 additional full-time employees for medical affairs, nine additional full-time employees for the regulatory and quality assurance function, three additional full-time employees for logistics and distribution and three additional full-time employees for general and administrative activities. Should we decide to market neratinib on our own, we would also hire approximately 130 additional full-time employees for sales, marketing and other commercial product launch activities.

In addition, we intend to continue to use CROs and third parties to perform our clinical studies and manufacturing.

Corporate Information and History

Our principal executive offices are located at 10880 Wilshire Boulevard, Suite 2150, Los Angeles, California 90024 and our telephone number is (424) 248-6500. Our internet address is *www.pumabiotechnology.com* . Our annual, quarterly and current reports, and any amendments to those reports, filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 may be accessed free of charge through our website after we have electronically filed or furnished such material with the SEC. We also make available free of charge on or through our website our Code of Business Conduct and Ethics, Corporate Governance Guidelines, Audit Committee Charter, Compensation Committee Charter and Nominating and Corporate Governance Committee Charter. We will disclose on a current report on Form 8-K or on our website information any amendment or waiver of the Code of Business Conduct and Ethics for our executive officers and directors. Any amendment or waiver disclosed on our website will remain available on our website for at least 12 months after the initial disclosure.

The reference to *www.pumabiotechnology.com* (including any other reference to such address in this Annual Report) is an inactive textual reference only, meaning that the information contained on or accessible from the website is not part of this Annual Report on Form 10-K and is not incorporated in this report by reference.

We were originally incorporated in the State of Delaware in April 2007 under the name Innovative Acquisitions Corp. We were a “shell” company registered under the Exchange Act with no specific business plan or purpose until we acquired Former Puma in the Merger. As a result of this transaction, Former Puma become our wholly-owned subsidiary and subsequently merged with and into us, at which time we adopted Former Puma’s business plan and changed our name to “Puma Biotechnology, Inc.”

The Merger was accounted for as a reverse acquisition whereby Former Puma was deemed to be the acquirer for accounting and financial reporting purposes and we were deemed to be the acquired party. Consequently, our financial statements prior to the Merger reflect the assets and liabilities and the historical operations of Former Puma from its inception on September 15, 2010, through the closing of the Merger on October 4, 2011. Our financial statements after completion of the Merger include the a ssets and liabilities of us and Former Puma, the historical operations of Former Puma, and the operations of us following the closing date of the Merger.

The merger of a private operating company into a non-operating public shell corporation with nominal net assets is considered to be a capital transaction, in substance, rather than a business combination, for accounting purposes. Accordingly, we treated this transaction as a capital transaction without recording goodwill or adjusting any of our other assets or liabilities.

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.

ITEM 1A. RISK FACTORS

In addition to the other information contained in this Annual Report, the following risk factors should be considered carefully in evaluating our company. Our business, financial condition, liquidity or results of operations could be materially adversely affected by any of these risks.

Risks Related to our Business

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

To date, we have generated no product revenues. Until, and unless, we receive approval from the FDA and other regulatory authorities overseas for one or more of our drug candidates, we cannot market or sell our products and will not have product revenues. Currently, our only drug candidates are neratinib (oral), neratinib (intravenous) and PB357, and none of these products has been approved by the FDA for sale in the United States or by other regulatory authorities for sale outside the United States. We do not expect to achieve any product revenues until neratinib is commercialized which could occur as early as the end of 2017, though we cannot assure you that we will commercialize neratinib this year or ever. Until we commercialize neratinib or another product candidate, we will continue to fund all of our operations and capital expenditures from cash on hand, licensing fees and grants, and potentially, future offerings of our securities.

We are currently exploring methods by which to commercialize our product candidates if approved by the FDA or EMA. These methods may require funding in addition to the cash and cash equivalents and marketable securities totaling approximately $229.4 million available at December 31, 2016. While our consolidated financial statements have been prepared on a going concern basis, we expect to continue incurring significant losses for the foreseeable future and will continue to remain dependent on our ability to obtain sufficient funding to sustain operation and successfully commercially launch neratinib if approved by the FDA or EMA. While we have been successful in raising financing in the past, there can be no assurance that we will be able to do so in the future. Our ability to obtain funding may be adversely impacted by uncertain market conditions, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time. If the going concern assumption was not appropriate for the preparation of our consolidated financial statements, adjustment might be necessary to the consolidated financial statements.

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

We were formed in April 2007 and were a “shell” company with no specific business plan or purpose until we acquired Former Puma on October 4, 2011. Former Puma was formed in September 2010 and, prior to entering into the license agreement with Pfizer in August 2011, its operations were limited to identifying compounds for in-licensing. As a result, we have a history of operating losses and no meaningful operations upon which to evaluate our business. We expect to incur substantial losses and negative operating cash flow for the foreseeable future as we continue development of our drug candidates. Even if we succeed in developing and commercializing one or more drug candidates, we expect to incur substantial losses for the foreseeable future and may never become profitable. The successful development and commercialization of any drug candidates will require us to perform a variety of functions, including:

- undertaking pre-clinical development and clinical trials;
- hiring additional personnel;
- participating in regulatory approval processes;
- formulating and manufacturing products;
- initiating and conducting sales and marketing activities; and
- implementing additional internal systems and infrastructure.

We will likely need to raise additional capital in order to fund our business and generate significant revenue in order to achieve and maintain profitability. We may not be able to generate this revenue, raise additional capital or achieve profitability in the future. Our failure to achieve or maintain profitability could negatively impact the value of our common stock.

Our independent registered public accounting firm has expressed substantial doubt about our ability to continue as a going concern.

Our historical consolidated financial statements have been prepared under the assumption that we will continue as a going concern. Our independent registered public accounting firm has issued a report on our audited consolidated financial statements for the year ended December 31, 2016 that included an explanatory paragraph referring to our significant operating losses and expressing substantial doubt in our ability to continue as a going concern. Our ability to continue as a going concern is dependent upon our ability to obtain additional equity financing or other capital, attain further operating efficiencies, reduce expenditures, and, ultimately, to generate revenue. Our consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. However, if adequate funds are not available to us when we need it, we will be required to curtail our operations which would, in turn, further raise substantial doubt about our ability to continue as a going concern. The doubt regarding our potential ability to continue as a going concern may adversely affect our ability to obtain new financing on reasonable terms or at all. Additionally, if we are unable to continue as a going concern, our stockholders may lose some or all of their investment in the Company.

We are heavily dependent on the success of neratinib (oral), our lead drug candidate, which is still under clinical development for various indications. While we have filed for regulatory approval of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, we cannot be certain that neratinib (oral) will receive regulatory approval for this or any other indication for which we may seek approval.

We currently have no products that are approved for commercial sale, and we may never be able to develop marketable drug products. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to the development of our lead drug candidate, neratinib (oral), in various indications. Accordingly, our business currently depends heavily on the successful development and regulatory approval of neratinib (oral). The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of drug products are and will remain subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries that each have differing regulations. We are not permitted to market neratinib (oral) or any of our drug candidates in the United States until they receive approval of an New Drug Application, or NDA, from the FDA, or in any foreign countries until they receive the requisite approval from such countries. We submitted an NDA with the FDA for regulatory approval of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer in the United States in July 2016 and a MAA with the European Medicines Agency, or EMA, in June 2016. Obtaining approval of an NDA is an extensive, lengthy, expensive and inherently uncertain process, and the FDA may delay, limit or deny approval of a drug candidate for many reasons, including:

- we may not be able to demonstrate that neratinib (oral) or any other drug candidate is safe and effective as a treatment for our targeted indications to the satisfaction of the FDA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA for marketing approval;
- the FDA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the clinical research organization, or CRO, that we retain to conduct clinical trials or any other third parties involved in the conduct of trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA may not find the data from pre-clinical studies and clinical trials sufficient to demonstrate that the clinical and other benefits of neratinib (oral) or any other drug candidate outweigh the safety risks;
- the FDA may disagree with our interpretation of data from our pre-clinical studies and clinical trials or may require that we conduct additional studies or trials;
- the FDA may not accept data generated at our clinical trial sites;
- if our NDA is reviewed by an advisory committee, the FDA may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of our application or may recommend that the FDA require, as a condition of approval, additional pre-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the advisory committee may recommend that the FDA require, as a condition of approval, additional pre-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy as a condition of approval;
- the FDA may identify deficiencies in the manufacturing processes or facilities of our third-party manufacturers; or
- the FDA may change its approval policies or adopt new regulations.

We currently have no sales, marketing or distribution capabilities. If we are unable to establish such capabilities on our own or through third parties, we may not be successful in commercializing nerati nib in the extended adjuvant indication or in any other indication if and when it is approved.

We currently have no sales, marketing or distribution capabilities and only a limited number of our employees have experience in marketing or selling pharmaceutical products. To achieve commercial success for any of our proposed products, if approved, we must either develop a direct sales, marketing and distribution organization or enter into arrangements with third parties to market, sell and distribute such products. We submitted a New Drug Application, or NDA, with the FDA for regulatory approval of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer in the United States in July 2016 and an MAA with the EMA in June 2016. We are continuing to evaluate potential commercialization options for neratinib in the extended adjuvant setting, including developing a direct sales force, contracting with third parties to provide sales and marketing capabilities, some combination of these two options or other strategic options. There are risks involved both with establishing our own sales and marketing capabilities and with entering into arrangements with third parties to perform these services. For example, any efforts to develop a direct sales and marketing organization would be subject to numerous risks, including:

- recruiting and training a sales force is expensive and time consuming and could delay any product launch;
- our inability to recruit, retain or motivate adequate numbers of effective and qualified sales and marketing personnel;
- the inability to provide adequate training to sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or convince adequate numbers of physicians to prescribe any future products;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- the premature or unnecessary incurrence of significant commercialization expenses if the commercial launch of a product is delayed or does not occur for any reason.

Similarly, if we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability associated with any product revenue may be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our proposed products or may be unable to do so on terms that are favorable to us. We may have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. Moreover, we may be negatively impacted by other factors outside of our control relating to such third parties, including, but not limited to, their inability to comply with regulatory requirements. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our proposed products.

Even if approved, we may not be able to successfully commercialize neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, which would have a material adverse impact on our business, results of operations and financial condition.

If approved, our near-term prospects, including our ability to generate revenue, will depend significantly on the successful commercialization of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer. Successful commercialization in this or any other indication for which we receive regulatory approval will depend on a number of factors, including the following:

- our ability to identify one or more third-party manufacturers that can produce commercial supplies of neratinib at a scale sufficient to meet our anticipated demand and on terms acceptable to us;
- the ability of our third-party manufacturers to develop, validate and maintain commercially viable manufacturing processes that are compliant with current Good Manufacturing Practice, or cGMP, regulations;
- our success in educating physicians and patients about the benefits, administration and use of neratinib;
- achieving and maintaining compliance with all regulatory requirements applicable to neratinib;
- acceptance of neratinib as safe and effective by patients and the medical community;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of alternative and competing treatments;
- our ability to avoid and defend against third-party patent interference or patent infringement claims;
- our ability to obtain and sustain an adequate level of reimbursement for neratinib by third-party payors;

- our ability to obtain, maintain, enforce and defend our intellectual property rights relating to neratinib and to comply with our obligations under, and otherwise maintain, our intellectual property license with Pfizer; and
- a continued acceptable safety profile of neratinib following approval.

If we are not successful in commercializing neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, or are significantly delayed in doing so, our business will be materially harmed.

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

Although we have submitted an NDA for regulatory approval for neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer in the United States in July 2016, our other drug candidates are still in development and will require extensive clinical testing before we can submit an NDA for regulatory approval. We cannot predict with any certainty that such NDA or any NDA submitted by us will be approved by the FDA. Human clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. The clinical trial process is also time-consuming. We estimate that clinical trials of our other drug candidates will take at least several years to complete. Furthermore, failure can occur at any stage of the trials, and we could encounter problems that cause us to abandon or repeat clinical trials. The results of pre-clinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful.

The commencement and completion of clinical trials may be delayed by several factors, including:

- imposition of a clinical hold or failure to obtain regulatory authorization or approval to commence a trial;
- unforeseen safety issues;
- determination of dosing issues;
- lack of effectiveness during clinical trials;
- inability to reach agreement on acceptable terms with prospective CROs and clinical trial sites;
- slower-than-expected rates of patient recruitment;
- failure to manufacture sufficient quantities of a drug candidate for use in clinical trials;
- inability to monitor patients adequately during or after treatment; and
- inability or unwillingness of medical investigators to follow our clinical protocols.

Further, we, the FDA or an Institutional Review Board, or IRB, may suspend our clinical trials at any time if it appears that we or our collaborators are failing to conduct a trial in accordance with regulatory requirements, that we are exposing participants to unacceptable health risks, or if the FDA finds deficiencies in our IND submissions or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our drug candidates could be harmed, and our ability to generate revenues from the drug candidates may be delayed. In addition, any delays in our clinical trials could increase our costs, slow down the approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and results of operations. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our drug candidates.

Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control.

We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and even once enrolled we may be unable to retain a sufficient number of patients to complete any of our trials. Patient enrollment and retention in clinical trials depends on many factors, including the size of the patient population, the nature of the trial protocol, the existing body of safety and efficacy data with respect to the study drug, the number and nature of competing treatments and ongoing clinical trials of competing drugs for the same indication, the proximity of patients to clinical sites and the eligibility criteria for the study. Furthermore, any negative results we may report in clinical trials of any of our drug candidates may make it difficult or impossible to recruit and retain patients in other clinical studies of that same drug candidate. Delays or failures in planned patient enrollment and/or retention may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop our drug candidates, or could render further development impossible. In addition, we expect to rely on CROs and clinical trial sites to ensure proper and timely conduct of our future clinical trials and, while we intend to enter into agreements governing their services, we will be limited in our ability to compel their actual performance.

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

Even if our clinical trials are completed as planned, we cannot be certain that their results will support the safety and effectiveness of our drug candidates for our targeted indications. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful, and we cannot be sure that the results of later clinical trials will replicate the results of prior clinical trials and pre-clinical testing. A failure of a clinical trial to meet its predetermined endpoints would likely cause us to abandon a drug candidate and may delay development of other drug candidates. Any delay in, or termination of, our clinical trials will delay the filing of our NDAs with the FDA and, ultimately, our ability to commercialize our drug candidates and generate product revenues.

While we have negotiated a special protocol assessment agreement with the FDA relating to our Phase III clinical study of PB272, this agreement does not guarantee approval of PB272 or any other particular outcome from regulatory review of the clinical trial or the drug candidate.

In February 2013, we announced that we reached agreement with the FDA under a Special Protocol Assessment, or SPA, for our Phase III clinical trial of PB272 in patients with HER2-positive metastatic breast cancer who have failed two or more prior treatments. We commenced the Phase III clinical trial in June 2013. The FDA's SPA process is designed to facilitate the FDA's review and approval of drugs by allowing the FDA to evaluate the proposed design and size of Phase III clinical trials that are intended to form the primary basis for determining a drug product's efficacy. Upon specific request by a clinical trial sponsor, the FDA will evaluate the protocol and respond to a sponsor's questions regarding, among other things, primary efficacy endpoints, trial conduct and data analysis, within 45 days of receipt of the request. The FDA ultimately assesses whether the protocol design and planned analysis of the trial are acceptable to support regulatory approval of the product candidate with respect to the effectiveness of the identified indication. All agreements between the FDA and the sponsor regarding an SPA must be clearly documented in writing, either in the form of an SPA letter or minutes of a meeting between the sponsor and the FDA at which the SPA agreement was reached. However, an SPA agreement does not guarantee approval of a product candidate, and even if the FDA agrees to the design, execution, and analysis proposed in protocols reviewed under the SPA process, the FDA may revoke or alter its agreement in certain circumstances. In particular, an SPA agreement is not binding on the FDA if public health concerns emerge that were unrecognized at the time of the SPA agreement, other new scientific concerns regarding product safety or efficacy arise, the sponsor company fails to comply with the agreed upon trial protocols, or the relevant data, assumptions or information provided by the sponsor in a request for the SPA change or are found to be false or omit relevant facts. In addition, even after an SPA agreement is finalized, the SPA agreement may be modified, and such modification will be deemed binding on the FDA review division, except under the circumstances described above, if the FDA and the sponsor agree in writing to modify the protocol and such modification is intended to improve the study. The FDA retains significant latitude and discretion in interpreting the terms of the SPA agreement and the data and results from any study that is the subject of the SPA agreement.

We cannot assure you that our Phase III clinical trial will succeed, or that the SPA will ultimately be binding on the FDA or will result in any FDA approval for PB272. The trial is expected to enroll approximately 600 patients. We expect that the FDA will review our compliance with the SPA, evaluate the results of the clinical trials and conduct inspections of some of the approximately 250 sites in North America, Europe and Asia-Pacific where the clinical trials will be conducted. We cannot assure you that each of the clinical trial sites will pass such FDA inspections, and negative inspection results could significantly delay or prevent any potential approval for PB272. If the FDA revokes or alters its agreement under the SPA, or interprets the data collected from the clinical trial differently than we do, the FDA may deem the data insufficient to support regulatory approval, which could materially adversely affect our business, financial condition and results of operations.

Our drug candida tes may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our drug candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. To date, subjects treated with our drug candidates have experienced drug-related side effects including diarrhea. Results of our trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Additionally if one or more of our drug candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Even if we receive regulatory approval for any of our drug candidates, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our drug candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials, and surveillance to monitor the safety and efficacy of the drug candidate. In addition, if the FDA or a comparable foreign regulatory authority approves any of our drug candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCPs for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or adm inistrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issu ance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, an d review and approval of marketing applications. Notably, on January 23, 2017, President Trump ordered a hiring freeze for all executive departments and agencies, including the FDA, which prohibits the FDA from filling employee vacancies or creating new po sitions. Under the terms of the order, the freeze will remain in effect until implementation of a plan to be recommended by the Director for the Office of Management and Budget, or OMB, in consultation with the Director of the Office of Personnel Managemen t, to reduce the size of the federal workforce through attrition. An under-staffed FDA could result in delays in FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Moreover, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, that requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This Executive Order includes a budget neutrality pro vision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agen cies to identify regulations to offset any incremental cost of a new regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB on February 2, 2017, the administration indicates that the "two-for-one" provisions m ay apply not only to agency regulations, but also to significant agency guidance documents. It is difficult to predict how these requirement will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authorit y. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Physicians and patients may not accept and use our drugs, if approved.

Even if the FDA approves one or more of our drug candidates, physicians and patients may not accept and use them. Acceptance and use of our product will depend upon a number of factors including:

- perceptions by members of the health care community, including physicians, about the safety and effectiveness of our drug;
- cost-effectiveness of our products relative to competing products;
- availability of coverage and reimbursement for our products from government or other healthcare payors; and
- effectiveness of marketing and distribution efforts by us and our licensees and distributors, if any.

Because we expect sales of our current drug candidates, if approved, to generate substantially all of our product revenues for the foreseeable future, the failure of these drugs to find market acceptance would harm our business and could require us to seek additional financing.

We rely on third parties to conduct our pre-clinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for our drug candidates.

We depend upon independent investigators and collaborators, such as CROs, universities and medical institutions, to conduct our pre-clinical studies and clinical trials under agreements with us. These collaborators are not our employees and we cannot control the amount or timing of resources that they devote to our programs. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with regulatory requirements, including good clinical practice, or GCP, requirements, and the applicable protocol. If we or any of our CROs or third party contractors fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practice, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, third party contractors and investigators may not assign as great a priority to our programs or pursue them as diligently as we would if we were undertaking such programs ourselves. If outside collaborators fail to devote sufficient time and resources to our drug-development programs, or if their performance is substandard or otherwise fails to satisfy applicable regulatory requirements, the approval of our FDA applications, if any, and our introduction of new drugs, if any, will be delayed. These collaborators may also have relationships with other commercial entities, some of whom may compete with us. If our collaborators assist our competitors to our detriment, our competitive position would be harmed. If any of our relationships with these third-party collaborators terminate, we may not be able to enter into arrangements with alternative third parties on commercially reasonable terms, or at all. Switching or adding additional third parties to our clinical trial programs can involve substantial costs and require extensive management time and focus.

We will rely exclusively on third parti es to formulate and manufacture our drug candidates. The commercialization of any of our drug candidates, if approved, could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of product or fail to do so at acceptable quality levels or prices .

We have no experience in drug formulation or manufacturing and do not intend to establish our own manufacturing facilities. We lack the resources and expertise to formulate or manufacture our own drug candidates. While our drug candidates were being developed by Pfizer, both the drug substance and drug product were manufactured by third-party contractors. We are using the same third-party contractors to manufacture, supply, store and distribute drug supplies for our clinical trials. If we are unable to continue our relationships with one or more of these third-party contractors, we could experience delays in our development efforts as we locate and qualify new manufacturers. We submitted an NDA with the FDA for regulatory approval of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer in the United States in July 2016 and a MAA with the European Medicines Agency, or EMA, in June 2016. If approved for this indication or if any of our other drug candidates receive regulatory approval, we will need to develop commercial manufacturing abilities. We intend to rely on one or more third-party contractors to manufacture the commercial supply of our drugs. Our anticipated future reliance on a limited number of third-party manufacturers exposes us to the following risks:

- We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and the FDA must approve any replacement manufacturer. This approval would require new testing and compliance inspections. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our products after receipt of FDA approval, if any.
- Our third-party manufacturers might be unable to formulate and manufacture our drugs in the volume and of the quality required to meet our clinical needs and commercial needs, if any.
- Our future contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store and distribute our products.
- The facilities used by our contract manufacturers to manufacture our drug candidates must be approved by the FDA pursuant to inspections that are conducted following submission of an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs, for manufacture of both active drug substances and finished drug products. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration for controlled substances, similar non-U.S. regulatory agencies and corresponding state agencies to ensure strict compliance with cGMP regulations and other government regulations and corresponding foreign standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our drug candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.
- If any third-party manufacturer makes improvements in the manufacturing process for our products, we may not own, or may have to share, the intellectual property rights to the innovation.

Each of these risks could delay our clinical trials, the approval, if any, of our drug candidates by the FDA or the commercialization of our drug candidates or result in higher costs or deprive us of potential product revenues.

We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively.

Our internal computer systems and those of third parties with which we contract may be vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures despite the implementation of security measures. System failures, accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our research and development programs and the development of our product candidates could be delayed.

Health care reform measures may hinder or prevent our drug candidates' commercial success.

The United States and some foreign jurisdictions have enacted or are considering enacting a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to profitably sell our products, if and when they are approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, became law in the United States. The ACA substantially changed and will continue to change the way healthcare is financed by both governmental and private insurers and significantly affects the pharmaceutical industry. Among the provisions of the ACA, of greatest importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals, which began in April 2010, and by adding new eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing manufacturers' Medicaid rebate liability;
- increase in the number of entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians;
- a licensure framework for follow-on biologic products; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

The ACA also requires adults not covered by employer or government-sponsored insurance plans to maintain health insurance coverage or pay a penalty, a provision commonly referred to as the individual mandate.

We expect that the new presidential administration and U.S. Congress will seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA.Since taking office, President Trump has continued to support the repeal of all or portions of the ACA. In January 2017, the House and Senate passed a budget resolution that authorizes congressional committees to draft legislation to repeal all or portions of the ACA and permits such legislation to pass with a majority vote in the Senate. President Trump has also recently issued an executive order in which he stated that it is his administration's policy to seek the prompt repeal of the ACA and directed executive departments and federal agencies to waive, defer, grant exemptions from, or delay the implementation of the provisions of the ACA to the maximum extent permitted by law. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by ACA However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments, will remain in effect through 2025 unless additional Congressional action is taken. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or ATRA, which,

among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to r ecover overpayments to providers from three to five years. Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquir ies and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. For example, the 21st Century Cures Act changes the reimbursement methodology for infusion drugs and biologics furnished through durable medical equipment in an attempt to remedy over- and underpayment of certain drugs. We cannot predict all of the ways in whi ch future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

Nevertheless, we anticipate that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Thus, we expect to experience pricing pressures in connection with the sale of neratinib (oral), neratinib (intravenous), PB357 and any other products that we may develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals. There may be additional pressure by payors and healthcare providers to use generic drugs that contain the active ingredients found in neratinib (oral), neratinib (intravenous), PB357 or any other drug candidates that we may develop. If we fail to successfully secure and maintain adequate coverage and reimbursement for our products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our products and expected revenue and profitability which would have a material adverse effect on our business, results of operations and financial condition.

We may be subject, directly or indirectly, to federal and state healthcare laws, including, but not limited to, fraud and abuse and false claims laws and regulations. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our drug candidates and begin commercializing those products in the United States, our operations will be subject directly or indirectly through our customers, to various state and federal fraud and abuse and other healthcare laws, including, without limitation, the federal Anti-Kickback Statute and federal False Claims Act and the state and foreign law equivalents of such laws. These laws may impact, among other things, our research and manufacturing activities as well as our proposed sales, marketing, and education programs.

The federal Anti-Kickback Statute prohibits persons from knowingly and willingly soliciting, offering, receiving or providing remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual, or the furnishing or arranging for a good or service, for which payment may be made under a federal healthcare program such as the Medicare and Medicaid programs. The Anti-Kickback Statute is broad and, despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Penalties for violations of the federal Anti-Kickback Statute include criminal penalties and civil sanctions such as fines, imprisonment and possible exclusion from Medicare, Medicaid and other federal healthcare programs. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, including private insurance programs.

The federal False Claims Act prohibits persons from knowingly filing, or causing to be filed, a false claim, or the knowing use of false statements, to obtain payment from the federal government. Suits filed under the False Claims Act, known as “qui tam” actions, can be brought by any individual on behalf of the government, and such individuals, commonly known as “whistleblowers,” may share in any amounts paid by the entity to the government in fines or settlement. The frequency of filing qui tam actions has increased significantly in recent years, causing greater numbers of pharmaceutical, medical device and other healthcare companies to have to defend False Claims Act actions. When it is determined that an entity has violated the False Claims Act, the entity may be required to pay up to three times the actual damages sustained by the government, plus civil penalties for each separate false claim. Various states have also enacted laws modeled after the federal False Claims Act.

We may also be subject to federal criminal healthcare fraud statutes that were created by the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA. The HIPAA health care fraud statute prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private payors. A violation of this statute is a felony and may result in fines, imprisonment and/or exclusion from government sponsored programs. The HIPAA false statements statute prohibits, among other things, knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation in connection with the delivery of or payment for healthcare benefits, items or services. A violation of this statute is a felony and may result in fines and/or imprisonment. Additionally, the civil monetary penalties statute imposes penalties against any person or entity that, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The ACA, among other things, amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes. A person or entity no longe r needs to have actua l knowledge of this statute or specific intent to violate it. In addition, the ACA pr ovides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraud ulent claim for purposes of the False Claims Act.

The ACA also enacted new provisions that require manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations. Manufacturers are required to submit reports to the government by the 90th day of each calendar year. In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians. Certain states mandate implementation of commercial compliance programs , impose restrictions on drug manufacturer marketing practices, and/or the tracking and reporting of pricing and marketing information as well as gifts, compensation and other remuneration to physicians.

We may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information.

Additionally, many foreign governments have laws comparable to those described above, including reporting requirements detailing interactions with and payments to healthcare providers.

We are unable to predict whether we could be subject to actions under any of these healthcare laws or other fraud and abuse laws, or the impact of such actions. If we are found to be in violation of any of the laws described above and other applicable state and federal fraud and abuse laws, we may be subject to penalties, including civil and criminal penalties, damages, fines, individual imprisonment, disgorgement, exclusion from government healthcare reimbursement programs and the curtailment or restructuring of our operations, any of which could have a material adverse effect on our business and results of operations.

If we cannot compete successfully for market share against other drug companies, we may not achieve sufficient product revenue and our business will suffer.

The market for our drug candidates is characterized by intense competition and rapid technological advances. If any of our drug candidates receives FDA approval, it will compete with a number of existing and future drugs and therapies developed, manufactured and marketed by others. Existing or future competing products may provide greater therapeutic convenience or clinical or other benefits for a specific indication than our products, or may offer comparable performance at a lower cost. In addition, a large number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting. If our products fail to capture and maintain market share, we may not achieve sufficient product revenue and our business will suffer.

We will compete against fully integrated pharmaceutical companies and smaller companies that are collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors have oncology compounds that have already been approved or are in development. In addition, many of these competitors, either alone or together with their collaborative partners, operate larger research and development programs or have substantially greater financial resources than we do, as well as significantly greater experience in the following:

- developing drugs;
- undertaking pre-clinical testing and clinical trials;
- obtaining FDA and other regulatory approvals of drugs;
- formulating and manufacturing drugs; and
- launching, marketing and selling drugs.

Our ability to generate product revenues will be diminished if our drugs sell for inadequate prices or patients are unable to obtain coverage or adequate levels of reimbursement.

Our ability to commercialize our drugs, alone or with collaborators, will depend in part on the extent to which reimbursement will be available from the following:

- government and health administration authorities;
- private health maintenance organizations and health insurers; and
- other healthcare payors.

Significant uncertainty exists as to the coverage and reimbursement status of newly approved healthcare products. Healthcare payors, including Medicare, are challenging the prices charged for medical products and services. Government and other healthcare payors increasingly attempt to contain healthcare costs by limiting both coverage and the level of reimbursement for drugs. Even if one of our drug candidates is approved by the FDA, insurance coverage may not be available, or reimbursement levels may be inadequate to cover such drug. If government and other healthcare payors do not provide adequate coverage and reimbursement for any of our products, once approved, market acceptance of such product could be reduced.

We may be exposed to liability claims associated with the use of hazardous materials and chemicals.

Our research and development activities may involve the controlled use of hazardous materials and chemicals. Although we believe that our safety procedures for using, storing, handling and disposing of these materials comply with federal, state and local laws and regulations, we cannot completely eliminate the risk of accidental injury or contamination from these materials. In the event of such an accident, we could be held liable for any resulting damages and any liability could materially adversely affect our business, financial condition and results of operations. In addition, the federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous or radioactive materials and waste products may require us to incur substantial compliance costs that could materially adversely affect our business, financial condition and results of operations.

The loss of one or more key members of our management team could adversely affect our business.

Our success and future growth depends to a significant degree on the skills and continued services of our management team, in particular Alan H. Auerbach, our Chief Executive Officer and President. If Mr. Auerbach resigns or becomes unable to continue in his present role and is not adequately replaced, our business operations could be materially adversely affected. We do not maintain “key man” life insurance for Mr. Auerbach.

If we are unable to hire additional qualified personnel, our ability to grow our business may be harmed.

As of December 31, 2016, we had 160 employees, including our Chief Executive Officer and President. Our future success depends on our ability to identify, attract, hire, train, retain and motivate other highly skilled scientific, technical, marketing, managerial and financial personnel. Although we will seek to hire and retain qualified personnel with experience and abilities commensurate with our needs, there is no assurance that we will succeed despite their collective efforts. Competition for personnel is intense, and any failure to attract and retain the necessary technical, marketing, managerial and financial personnel would have a material adverse effect on our business, prospects, financial condition and results of operations.

We may not successfully manage our growth.

Our success will depend upon the expansion of our operations and our ability to successfully manage our growth. Our future growth, if any, may place a significant strain on our management and on our administrative, operational and financial resources. Our ability to manage our growth effectively will require us to implement and improve our operational, financial and management systems and to expand, train, manage and motivate our employees. These demands may require the hiring of additional management personnel and the development of additional expertise by management. Any increase in resources devoted to research and product development without a corresponding increase in our operational, financial and management systems could have a material adverse effect on our business, financial condition and results of operations.

We may be adversely affected by the current economic environment.

Our ability to attract and retain collaborators or customers, invest in and grow our business and meet our financial obligations depends on our operating and financial performance, which, in turn, is subject to numerous factors, including the prevailing economic conditions and financial, business and other factors beyond our control, such as the rate of unemployment, the number of uninsured persons in the United States and inflationary pressures. We cannot anticipate all the ways in which the current economic climate and financial market conditions could adversely impact our business.

We are exposed to risks associated with reduced profitability and the potential financial instability of our collaborators or customers, many of which may be adversely affected by volatile conditions in the financial markets. For example, unemployment and underemployment, and the resultant loss of insurance, may decrease the demand for healthcare services and pharmaceuticals. If fewer patients are seeking medical care because they do not have insurance coverage, our collaboration partners or customers may experience reductions in revenues, profitability and/or cash flow that could lead them to modify, delay or cancel orders for our products once commercialized. If collaboration partners or customers are not successful in generating sufficient revenue or are precluded from securing financing, they may not be able to pay, or may delay payment of, accounts receivable that are owed to us. This, in turn, could adversely affect our financial condition and liquidity. In addition, if economic challenges in the United States result in widespread and prolonged unemployment, either regionally or on a national basis, prior to the effectiveness of certain provisions of the ACA, a substantial number of people may become uninsured or underinsured. To the extent economic challenges result in fewer individuals pursuing or being able to afford our products once commercialized, our business, results of operations, financial condition and cash flows could be adversely affected.

We may incur substantial liabilities and may be required to limit commercialization of our products in response to product liability lawsuits.

The testing and marketing of medical products entail an inherent risk of product liability. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our products. If we are unable to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims, the commercialization of pharmaceutical products we develop, alone or with collaborators, could be prevented or inhibited.

Our cash and cash equivalents could be adversely affected if the financial institutions in which we hold our cash and cash equivalents fail.

We regularly maintain cash balances at third-party financial institutions in excess of the Federal Deposit Insurance Corporation, or FDIC, insurance limit. While we monitor daily the cash balances in the operating accounts and adjust the balances as appropriate, these balances could be impacted, and there could be a material adverse effect on our business, if one or more of the financial institutions with which we deposit fails or is subject to other adverse conditions in the financial or credit markets. To date, we have experienced no loss or lack of access to our invested cash or cash equivalents; however, we can provide no assurance that access to our invested cash and cash equivalents will not be impacted by adverse conditions in the financial and credit markets.

Our investments in marketable securities are subject to market, interest and credit risk that may reduce their value.

The value of our investments in marketable securities may be adversely affected by changes in interest rates, downgrades in the creditworthiness of bonds we hold, turmoil in the credit markets and financial services industry and by other factors which may result in other than temporary declines in the value of our investments. Decreases in the market value of our marketable securities could have an adverse impact on our consolidated financial statements, results of operations and cash flow.

Risks Related to Our Intellectual Property

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

We depend significantly on our license agreement with Pfizer. Our license agreement with Pfizer may be terminated by Pfizer if we materially breach the agreement and fail to cure our breach during an applicable cure period. Our failure to use commercially reasonable efforts to develop and commercialize licensed products in certain specified major market countries would constitute a material breach of the license agreement. Pfizer may also terminate the license agreement if we become involved in bankruptcy, receivership, insolvency or similar proceedings. In the event our license agreement with Pfizer is terminated, we will lose all of our rights to develop and commercialize the drug candidates covered by such license, which would significantly harm our business and future prospects.

Our proprietary rights may not adequately protect our intellectual property and potential products, and if we cannot obtain adequate protection of our intellectual property and po tential products, we may not be able to successfully market our potential products.

Our commercial success will depend in part on obtaining and maintaining intellectual property protection for our products, formulations, processes, methods and other technologies. We will only be able to protect these technologies and products from unauthorized use by third parties to the extent that valid and enforceable intellectual property rights, including patents, cover them, or other market exclusionary rights apply. The patent positions of pharmaceutical companies, like ours, can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The general environment for pharmaceutical patents outside the United States also involves significant uncertainty. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced, or that the scope of these patent rights could provide a sufficient degree of future protection that could permit us to gain or keep our competitive advantage with respect to these products and technology. For example, we cannot predict:

- the degree and range of protection any patents will afford us against competitors, including whether third parties will find ways to make, use, sell, offer to sell or import competitive products without infringing our patents;
- if and when patents will issue;
- whether or not others will obtain patents claiming inventions similar to those covered by our patents and patent applications; or
- whether we will need to initiate litigation or administrative proceedings in connection with patent rights, which may be costly whether we win or lose.

The patents we have licensed may be subject to challenge and possibly invalidated or rendered unenforceable by third parties. Changes in either the patent laws or in the interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property.

In addition, others may independently develop similar or alternative products and technologies that may be outside the scope of our intellectual property. Furthermore, others may have invented technology claimed by our patents before we or our licensors did so, and they may have filed patents claiming such technology before we did so, weakening our ability to obtain and maintain patent protection for such technology. Should third parties obtain patent rights to similar products or technology, this may have an adverse effect on our business.

We may also rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or obtainable. Trade secrets, however, are difficult to protect. While we believe that we will use reasonable efforts to protect our trade secrets, our own or our strategic partners' employees, consultants, contractors or advisors may unintentionally or willfully disclose our information to competitors. We seek to protect this information, in part, through the use of non-disclosure and confidentiality agreements with employees, consultants, advisors and others. These agreements may be breached, and we may not have adequate remedies for a breach. In addition, we cannot ensure that those agreements will provide adequate protection for our trade secrets, know-how or other proprietary information or prevent their unauthorized use or disclosure.

To the extent that consultants or key employees apply technological information independently developed by them or by others to our potential products, disputes may arise as to the proprietary rights in such information, which may not be resolved in our favor. Consultants and key employees who work with our confidential and proprietary technologies are required to assign all intellectual property rights in their discoveries to us. However, these consultants or key employees may terminate their relationship with us, and we cannot preclude them indefinitely from dealing with our competitors. If our trade secrets become known to competitors with greater experience and financial resources, the competitors may copy or use our trade secrets and other proprietary information in the advancement of their products, methods or technologies. If we were to prosecute a claim that a third party had illegally obtained and was using our trade secrets, it could be expensive and time consuming and the outcome could be unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets than courts in the United States. Moreover, if our competitors independently develop equivalent knowledge, we would lack any legal or contractual claim to prevent them from using such information, and our business could be harmed.

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 that litigation would have a material adverse effect on our business.

Our ability to commercialize our potential products will depend on our ability to sell such products without infringing the patents or other proprietary rights of third parties. Third-party intellectual property rights in our field are complicated and continuously evolving. The coverage of patents is subject to interpretation by the courts, and this interpretation is not always consistent.

Other companies may have or may acquire intellectual property rights that could be enforced against us. If they do so, we may be required to alter our products, formulations, processes, methods or othe r technologies, obtain a license, assuming one can be obtained, or cease our product-related activities. If our products or technologies infringe the intellectual property rights of others, they could bring legal action against us or our licensors or colla borators claiming damages and seeking to enjoin any activities that they believe infringe their intellectual property rights. If we are sued for patent infringement, we would need to demonstrate that our products or methods of use either do not infringe th e patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving the invalidity of a patent is particularly difficult in the United States, since it requires a showing of clear and co nvincing evidence to overcome the presumption of validity enjoyed by issued patents. If we are found to infringe a third-party patent, we may need to cease the commercial sale of our products.

Because patent applications can take many years to issue, there may be currently pending applications unknown to us or reissue applications that may later result in issued patents upon which our products or technologies may infringe. There could also be existing patents of which we are unaware that our products or technologies may infringe. In addition, if third parties file patent applications or obtain patents claiming products or technologies also claimed by us in pending applications or issued patents, we may have to participate in interference proceedings in the U.S. Patent and Trademark Office, or USPTO, to determine priority of invention. If third parties file oppositions in foreign countries, we may also have to participate in opposition proceedings in foreign tribunals to defend the patentability of our filed foreign patent applications. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Additionally, any uncertainties resulting from the initiation and continuation of any litigation may have a material adverse effect on our ability to raise the funds necessary to continue our operations.

If a third party claims that we infringe its intellectual property rights, it could cause our business to suffer in a number of ways, including:

- we may become involved in time-consuming and expensive litigation, even if the claim is without merit, the third party's patent is ultimately invalid or unenforceable, or we are ultimately found to have not infringed;
- we may become liable for substantial damages for past infringement if a court decides that our technologies infringe upon a third party's patent;
- we may be ordered by a court to stop making, selling or licensing our products or technologies without a license from a patent holder, and such license may not be available on commercially acceptable terms, if at all, or may require us to pay substantial royalties or grant cross-licenses to our patents; and
- we may have to redesign our products so that they do not infringe upon others' patent rights, which may not be possible or could require substantial investment and/or time.

If any of these events occur, our business could suffer and the market price of our common stock may decline.

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other companies in these industries, including our competitors or potential competitors. We may become subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers, although no such claims are pending. Litigation may be necessary to defend against these claims. Even if we successfully defend any such claims, we may incur substantial costs in such defense, and our management may be distracted by these claims.

Risks Related to Owning our Common Stock

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.

Since January 2, 2017, our common stock has been listed on the NASDAQ Global Select Market, or NASDAQ. Prior to January 2, 2017, shares of our common stock had been listed on the New York Stock Exchange, or NYSE, 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 NASDAQ 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, 2016, we had 36,826,010 shares of common stock outstanding and stockholders holding at least 5% of our stock, individually or with affiliated entities, collectively owned or controlled approximately 65.9% of such shares. Sales of large numbers of shares by any of our large stockholders could adversely affect our trading price. 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 a less active trading market, 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 regarding results of any clinical trials relating to our drug candidates;
- announcements of medical innovations or new products by our competitors;
- 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;
- 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 biotechnology 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.

Volatility in the price of our common stock may subject us to securities litigation., which could cause us to incur substantial costs and divert management's attention, financial resources and other company assets.

In the past, securities class action litigation has often been brought against a company following periods of volatility in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. On June 3, 2015, we and certain of our executive officers were named as defendants in a securities class action lawsuit. The amended complaint, filed on October 16, 2015, on behalf of all persons who purchased our securities between July 22, 2014 and May 29, 2015, generally alleges that we and such executive officers made false and/or misleading statements and failed to disclose material adverse facts about our business, operations, prospects and performance. On April 12 and April 14, 2016, alleged shareholders filed two derivative lawsuits purportedly on behalf of the Company against certain of our officers and directors. The complaints assert claims for breach of fiduciary duty, unjust enrichment, abuse of control, mismanagement and waste of corporate assets arising from substantially similar allegations as those contained in the putative securities class action described above. These lawsuits and any future lawsuits to which we may become a party are subject to inherent uncertainties and will likely be expensive and time-consuming to investigate, defend and resolve, and will divert our management's attention and financial and other resources. The outcome of litigation is necessarily uncertain, and we could be forced to expend significant resources in the defense of this and other suits, and we may not prevail. Any litigation to which we are a party may result in an onerous or unfavorable judgment that may not be reversed upon appeal or in payments of substantial monetary damages or fines, or we may decide to settle this or other lawsuits on similarly unfavorable terms, which could adversely affect our business, financial condition, results of operations or stock price. See Item 3. "Legal Proceedings" below for additional information regarding the class action.

Issuance of stock to fund our operations may dilute your investment and reduce your equity interest.

We may need to raise capital in the future to fund the development of our drug candidates or for other purposes. Any equity financing may have a significant dilutive effect to stockholders and a material decrease in our existing stockholders' equity interest in us. Equity financing, if obtained, could result in substantial dilution to our existing stockholders. At its sole discretion, our board of directors may issue additional securities without seeking stockholder approval, and we do not know when we will need additional capital or, if we do, whether it will be available to us.

Upon the exercise of our outstanding warrant, holders of our common stock may experience immediate dilution and the market pric e of our common stock may be adversely affected.

Following an October 2011 private placement, Alan H. Auerbach, our founder, Chief Executive Officer and President, held approximately 21% of our outstanding shares of common stock. Pursuant to the terms of the Securities Purchase Agreement for the private placement, we issued an anti-dilutive warrant to Mr. Auerbach. The warrant has a 10-year term expiring in October 2021 for 2,116,250 shares with an exercise price of $16.00 per share.

If any portion of the outstanding warrant is exercised for shares of our common stock, our stockholders may experience immediate dilution and the market price of our common stock may be adversely affected.

We will incur increased costs and demands upon management as a result of complying with the laws and regulations affecting public companies, which could harm our operating results.

As a public company, we incur significant legal, accounting and other expenses, including costs associated with public company reporting requirements. We also incur costs associated with current corporate governance requirements, including requirements under Section 404 and other provisions of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, as well as rules implemented by the Securities and Exchange Commission, or the SEC, or NASDAQ or any stock exchange or inter-dealer quotations system on which our common stock may be listed in the future. The expenses incurred by public companies for reporting and corporate governance purposes have increased dramatically in recent years. We expect these rules and regulations to increase our legal and financial compliance costs and to make some activities more time-consuming and costly. We are unable to currently estimate these costs with any degree of certainty. We also expect that these rules and regulations may make it difficult and expensive for us to maintain the appropriate level of director and officer insurance for a company with our market capitalization. If we are unable to maintain an appropriate level of such insurance, we may be required to accept reduced policy limits and coverage or larger deductible limits. As a result, it may be more difficult for us to attract and retain qualified individuals to serve on our board of directors or as our executive officers.

If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, our ability to operate our business and investors' views of us.

We are subject to the rules and regulations of the SEC, including those rules and regulations mandated by the Sarbanes-Oxley Act. Section 404 of the Sarbanes-Oxley Act requires public companies to include in their annual report a statement of management's responsibilities for establishing and maintaining adequate internal control over financial reporting, together with an assessment of the effectiveness of those internal controls. Section 404 also requires the independent auditors of certain public companies to attest to, and report on, this management assessment. Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that will need to be evaluated frequently. Our failure to maintain the effectiveness of our internal controls in accordance with the requirements of the Sarbanes-Oxley Act could have a material adverse effect on our business. We could lose investor confidence in the accuracy and completeness of our financial reports, which could have an adverse effect on the price of our common stock. In addition, if our efforts to comply with new or changed laws, regulations, and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

Sales of a substantial number of shares of our common stock in the public market could cause the market price of our common stock to drop significantly, even if our business is doing well, which result would in turn negatively affect our ability to raise additional equity capital.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. A substantial majority of the outstanding shares of our common stock are freely tradable without restriction or further registration under the Securities Act of 1933, as amended. We have also registered all shares of common stock that we may issue under our equity compensation plan, which can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates. We are unable to predict the effect that sales may have on the prevailing market price of our common stock. However, an adverse effect on the market price of our common stock could have a material adverse effect on our ability to raise additional equity capital.

If securities or industry analysts do not publish, or cease publish ing, research or reports about us, our business or our market, or if they change their recommendations regarding our stock adversely, our stock price and trading volume could decline.

The trading market for our common stock is and will be influenced by whether industry or securities analysts publish research and reports about us, our business, our market or our competitors and, if any analysts do publish such reports, what they publish in those reports. We may not obtain analyst coverage in the future. Any analysts who do cover us may make adverse recommendations regarding our stock, adversely change their recommendations from time to time, and/or provide more favorable relative recommendations about our competitors. If any analyst who may cover us in the future were to cease coverage of our company or fail to regularly publish reports on us, or if analysts fail to cover us or publish reports about us at all, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

We do not foresee paying cash dividends in the foreseeable future.

We currently intend to retain any future earnings for funding growth. We do not anticipate paying any dividends in the foreseeable future. As a result, you should not rely on an investment in our securities if you require dividend income. Capital appreciation, if any, of our shares may be your sole source of gain for the foreseeable future. Moreover, you may not be able to re-sell your shares in us at or above the price you paid for them.

Our ability to use our net operating losses and research and development credit carryforwards to offset future taxable income may be subject to certain limitations.

In general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, and its research and development credit carryforwards to offset future taxable income. Our existing NOLs and research and development credit carryforwards may be subject to limitations arising from previous ownership changes, and if we undergo an ownership change, our ability to utilize NOLs and research and development credit carryforwards could be further limited by Sections 382 and 383 of the Code. Future changes in our stock ownership, some of which might be beyond our control, could result in an ownership change under Sections 382 and 383 of the Code. Furthermore, our ability to utilize NOLs and research and development credit carryforwards of any companies we may acquire in the future may be subject to limitations, in accordance with Sections 382 and 383 of the Code. For these reasons, in the event we experience a change of control, we may not be able to utilize a material portion of the NOLs and research and development credit carryforwards, even if we attain profitability.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

We lease approximately 25,700 square feet of office space in the building located at 10880 Wilshire Boulevard, Los Angeles, California for use as our corporate headquarters. This lease commenced in December 2011 and over time has been amended to add rentable square footage. In July 2015, we amended this lease to expand the leased space by approximately 26,000 square feet. The lease of the additional office space commenced on April 1, 2016. The lease terminates in March 2026, with an option to extend for an additional five-year term. We also lease approximately 9,600 square feet of office space in the building located at 701 Gateway Blvd, South San Francisco, California. The lease for the South San Francisco facility commenced in October 2012. In May 2014, the lease was amended to include approximately an additional 7,100 square feet of office space. In July 2015, we amended this office lease to expand the leased spaced by approximately 13,000 square feet. The lease commenced on April 1, 2016. The lease will terminate around March 2026, with an option to extend for an additional five-year term. We believe that our existing office space, along with the additional office space in South San Francisco, is adequate to meet current and anticipated future requirements and that additional or substitute space will be available as needed to accommodate any expansions that our operations require.

ITEM 3. LEGAL PROCEEDINGS

Hsu vs. Puma Biotechnology, Inc., et. al.

On June 3, 2015, Hsingching Hsu, individually and on behalf of all others similarly situated, filed a class action lawsuit against us and certain of our executive officers in the United States District Court for the Central District of California (Case No. 8:15-cv-00865-AG-JCG). On October 16, 2015, lead Plaintiff Norfolk Pension Fund filed an amended complaint on behalf of all persons who purchased our securities between July 22, 2014 and May 29, 2015. The amended complaint alleges that we and certain of our executive officers made false and/or misleading statements and failed to disclose material adverse facts about our business, operations, prospects and performance in violation of Sections 10(b) (and Rule 10b-5 promulgated thereunder) and 20(a) of the Exchange Act. The plaintiff seeks damages, interest, costs, attorneys' fees, and other unspecified equitable relief. On November 30, 2015, we filed a motion to dismiss the amended complaint. The plaintiff opposed this motion, and the court heard oral argument on March 14, 2016. On September 30, 2016, the court denied our motion to dismiss. The court set a trial for November 6, 2018. We intend to vigorously defend this matter.

Eshelman vs. Puma Biotechnology, Inc., et. al.

On February 2, 2016, Fredric N. Eshelman filed a lawsuit against our Chief Executive Officer and President, Alan H. Auerbach, and us in the United States District Court for the Eastern District of North Carolina (Case No. 7:16-cv-00018-D). The complaint generally alleges that Mr. Auerbach and we made defamatory statements regarding Dr. Eshelman in connection with a proxy contest. Dr. Eshelman seeks compensatory and punitive damages and expenses and costs, including attorneys' fees. On April 4, 2016, we filed a motion to dismiss the complaint. On May 2, 2016, Dr. Eshelman filed a notice of voluntary dismissal of the claims against Mr. Auerbach. On February 6, 2017, the court denied our motion to dismiss. On February 21, 2017, we filed an answer to Dr. Eshelman's complaint and brought counterclaims against Dr. Eshelman for defamatory statements regarding the Company made by him in connection with the proxy contest. The court has set a schedule for discovery to be conducted through September 2017. We intend to vigorously defend against Dr. Eshelman's claims and pursue our claims against him.

Derivative Actions

On April 12 and April 14, 2016, alleged shareholders filed two derivative lawsuits purportedly on behalf of the Company against certain of our officers and directors in the Superior Court of the State of California, Los Angeles, captioned Xing Xie v. Alan H. Auerbach, et al., No. BC616617, and Kevin McKenney v. Auerbach, et al., No. BC617059. The complaints assert claims for breach of fiduciary duty, unjust enrichment, abuse of control, mismanagement and waste of corporate assets arising from substantially similar allegations as those contained in the putative securities class action described above. The complaints seek an unspecified sum of damages and equitable relief. We intend to vigorously defend this matter.

The pending proceedings described in this section involve complex questions of fact and law and will require the expenditure of significant funds and the diversion of other resources to defend. The results of legal proceedings are inherently uncertain, and material adverse outcomes are possible.

I TEM 4. MINE SAFETY DISCLOSURE

Not applicable.

Part II

I TEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market for Common Stock

Our common stock has been quoted on the NASDAQ Global Select Market, or NASDAQ, since January 2, 2017. Prior to January 2, 2017, shares of our common stock had been listed on the New York Stock Exchange, or NYSE, since October 19, 2012. The high and low sales prices of our common stock on NYSE are set forth below for the periods indicated:

2016	High	Low
First quarter	$ 77.99	$ 25.20
Second quarter	39.67	19.74
Third quarter	73.27	28.14
Fourth quarter	68.05	29.85

2015	High	Low
First quarter	$ 252.92	$ 183.50
Second quarter	244.90	112.32
Third quarter	119.36	70.39
Fourth quarter	94.93	56.11

On February 22, 2017, the last reported sale price for our common stock on NASDAQ was $34.30 per share.

Record Holders

On January 9, 2017, we had 19 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities. We believe approximately 10,463 additional owners held our common stock in "Street Name" as of January 9, 2017.

Dividends

We have never 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 in 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.

Securities Authorized for Issuance Under Equity Compensation Plans

The information included under Item 12 of Part III of this Annual Report, "Securities Authorized for Issuance Under Equity Compensation Plans," is hereby incorporated by reference into this Item 5 of Part II of this Annual Report.

Recent Sales of Unregistered Securities

We did not make any sales of unregistered securities during fiscal year 2016.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

Neither we nor any "affiliated purchasers" within the definition of Rule 10b-18(a)(3) made any purchases of our equity securities during the fourth quarter of 2016.

ITEM 6. SELECTED FINANCIAL DATA

The following financial data should be read in conjunction with our consolidated financial statements and the related notes thereto appearing elsewhere in this Annual Report and with the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations."

The Consolidated Statements of Operations Data and Other Financial Data for the years ended December 31, 2016, 2015 and 2014, and the Consolidated Balance Sheet Data as of December 31, 2016 and 2015 have been derived from our audited consolidated financial statements included elsewhere in this Annual Report. The Consolidated Statement of Operations Data and Other Financial Data for the year ended December 31, 2013 and 2012, and the Consolidated Balance Sheet Data as of December 31, 2014, 2013 and 2012, have been derived from our audited consolidated financial statements not included herein. Historical results are not necessarily indicative of the results to be expected in the future, and the results for the years presented should not be considered indicative of our future results of operations.

	Years Ended December 31,				
	2016	2015	2014	2013	2012
	(in millions, except share and per share data)				
Statement of Operations Data:					
Expenses:					
General and administrative	$ 53.8	$ 31.8	$ 19.4	$ 9.8	$ 24.8
Research and development	222.8	208.5	122.9	45.0	49.6
Operating loss	(276.6)	(240.3)	(142.3)	(54.8)	(74.4)
Interest income	1.0	1.0	0.3	0.2	0.1
Other income	(0.4)	—	—	—	—
Totals	0.6	1.0	0.3	0.2	0.1
Net loss	(276.0)	(239.3)	(142.0)	(54.6)	(74.3)
Net loss attributable to common stock	(276.0)	(239.3)	(142.0)	(54.6)	(74.3)
Net loss per common share—basic and diluted	(8.29)	(7.45)	(4.73)	(1.90)	(3.42)
Weighted-average common shares outstanding—basic and diluted	33,295,114	32,126,094	30,010,979	28,696,573	21,725,986

	As of December 31,				
	2016	2015	2014	2013	2012
	(in millions)				
Balance Sheet Data:					
Total assets	$ 252.8	$ 239.8	$ 162.8	$ 104.4	$ 151.7
Total liabilities	43.0	33.8	45.7	20.4	22.8
Total stockholders' equity	209.8	206.0	117.0	84.0	128.9

	Years Ended December 31,				
	2016	2015	2014	2013	2012
	(in millions)				
Other Financial Data:					
Net cash used in operating activities	$ (141.7)	$ (154.5)	$ (77.2)	$ (55.0)	$ (44.0)
Net cash provided by (used in) investing activities	142.2	(85.9)	(63.3)	(41.5)	(1.2)
Net cash provided by financing activities	162.4	233.4	136.0	2.2	129.3

I tem 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

This Annual Report on Form 10-K contains forward-looking statements within the meanings of the federal securities laws. These statements are subject to risks and uncertainties that could cause actual results and events to differ materially from those expressed or implied by such forward-looking statements. For a detailed discussion of these risks and uncertainties, see the "Risk Factors" section in Item 1A of Part I of this Form 10-K. We caution the reader not to place undue reliance on these forward-looking statements, which reflect management's analysis only as of the date of this Form 10-K. We undertake no obligation to update forward-looking statements to reflect events or circumstances occurring after the date of this Form 10-K.

Overview

We are a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. We in-license the global development and commercialization rights to three drug candidates—PB272 (neratinib (oral)), PB272 (neratinib (intravenous)) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor, or TKI, that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Currently, we are primarily focused on the development of the oral version of neratinib, and our most advanced drug candidates are directed at the treatment of HER2-positive breast cancer. We believe neratinib has clinical application in the treatment of several other cancers as well, including non-small cell lung cancer and other tumor types that over-express or have a mutation in HER2. Our efforts and resources to date have been focused primarily on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel. We have had no product sales to date and we will have no product sales until we receive approval from the United States Food and Drug Administration, or FDA, or equivalent foreign regulatory bodies to begin selling a drug product. Developing drug products, however, is a lengthy and very expensive process. Assuming we do not encounter any unforeseen safety issues during the course of developing our drug candidates, we do not expect to receive approval of a product candidate until approximately the second half of 2017, though we cannot assure you that we will receive approval for any of our drug candidates this year or ever.

We recently completed a Phase III clinical trial of neratinib for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, which we refer to as the ExteNET trial. Based on the results from the ExteNET trial, we submitted a New Drug Application, or NDA, with the FDA for regulatory approval of neratinib in the extended adjuvant setting in the United States in July 2016 and a Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, in June 2016. We are continuing to evaluate potential commercialization options for neratinib in this indication, including developing a direct sales force, contracting with third parties to provide sales and marketing capabilities, some combination of these two options or other strategic options. We expect that our expenses will continue to increase as we continue to evaluate our options with regard to commercialization efforts.

The license agreement for PB272 established a limit for our expenses related to the Pfizer-initiated clinical trials for PB272 that were ongoing at the time of the agreement. This capped our "out-of-pocket" costs incurred in conducting these existing trials beginning January 1, 2012. We reached the cost cap during the fourth quarter of 2012, which resulted in a reduction of our research and development, or R&D, expenses for the fourth quarter of 2012 and for the year ended December 31, 2013. In July 2014 the Company signed an amendment to the license agreement with the Licensor whereby the Company would be responsible for the expenses incurred or accrued in conducting the ongoing legacy clinical trials after December 31, 2013. Additionally, our expenses to date have been related to hiring staff, commencing company-sponsored clinical trials and the build out of our corporate infrastructure. As we proceed with clinical development of PB272 (neratinib (oral)), and as we further develop PB272 (neratinib (intravenous)), and PB357, our second and third product candidates, respectively, we expect our R&D expenses and expenses related to our third-party contractors will continue to increase.

To the extent we are successful in acquiring additional product candidates for our development pipeline, our need to finance R&D will increase. Accordingly, our success depends not only on the safety and efficacy of our product candidates, but also on our ability to finance product development. Our major sources of working capital have been proceeds from public offerings of our common stock and sales of our common stock in private placements.

Summary of Expenses

General and administrative, or G&A, expenses consist primarily of salaries and related personnel costs, including stock-based compensation expense, professional fees, business insurance, rent, general legal activities, and other corporate expenses.

R&D expenses include costs associated with services provided by consultants who conduct clinical services on our behalf, contract organizations for manufacturing of clinical materials and clinical trials. During the years ended December 31, 2016, 2015 and 2014, our R&D expenses consisted primarily of clinical research organization, or CRO, fees; fees paid to consultants; salaries and related personnel costs; and stock-based compensation. We expense our R&D costs as they are incurred.

Results of Operations

The following summarizes our results of operations for the years ended December 31, 2016, 2015 and 2014.

General and administrative expenses:

General and administrative expenses (in thousands)	2016	2015	2014	Annual percentage change 2016/2015	2015/2014
Payroll and related costs	$ 7,004	$ 4,226	$ 3,323	65.7%	27.2%
Professional fees and expenses	12,604	5,522	3,304	128.3%	67.1%
Facility and equipment costs	4,568	2,376	1,754	92.3%	35.5%
Employee stock-based compensation expense	26,623	17,166	9,154	55.1%	87.5%
Other	2,999	2,518	1,823	19.1%	38.1%
	$ 53,798	$ 31,808	$ 19,358	69.1%	64.3%

Year Ended December 31, 2016 Compared to Year Ended December 31, 2015

Total G&A expenses increased approximately 69.1% to $53.8 million for the year ended December 31, 2016 from $31.8 million for the year ended December 31, 2015. Approximately $9.4 million of this increase, or 42.7% of the total increase, is related to an increase in stock-based compensation expense, attributable to our increased headcount and additional incentive awards to existing employees. The remaining approximately $12.6 million increase in G&A expense for the year ended December 31, 2016 compared to the same period in 2015 was primarily attributable to:

- An approximately $7.1 million increase in professional fees and expenses, which consist primarily of legal, auditing, consulting and investor relations fees. Included in this expense is approximately $5.3 million in consulting and professional expense for our pre-commercialization efforts. We expect professional fees and expenses to increase as we prepare for commercial product launch, continue to defend against the pending class action, derivative and defamation lawsuits filed against us and as we continue to implement compliance measures related to the Sarbanes-Oxley Act of 2002, as amended, or Sarbanes-Oxley.
- An approximately $2.8 million increase in payroll and related costs as administrative headcount increased from 18 to 27. Of this increase, approximately $2.1 million of the increase was in support of the potential commercial product launch which we anticipate could occur as early as the end of 2017, though we cannot assure you that we will commercialize any product this year or ever.
- An approximately $2.2 million increase in facility and equipment costs. As described in Note 9—Commitments and Contingencies to our consolidated financial statements included in this report, we amended two of our office leases, which took effect in April 2016. We expect our facility and equipment costs will increase only slightly, pursuant to the terms of those amended leases which were not in effect a full year during 2016.
- An approximately $0.5 million increase in other expenses primarily attributable to supporting our corporate growth.

In addition to the above items, we expect G&A expense will continue to increase as we continue to evaluate our options with regard to commercialization efforts during 2017 and beyond.

Year Ended December 31, 2015 Compared to Year Ended December 31, 2014

Total G&A expenses increased approximately 64.3% to $31.8 million for the year ended December 31, 2015 from $19.4 million for the year ended December 31, 2014. Approximately $8.0 million of this increase, or 64.4% of the total increase, is related to an increase in stock-based compensation expense, attributable to our increased headcount and additional incentive awards to existing employees. The remaining approximately $4.4 million increase in G&A expense for the year ended December 31, 2015 compared to the same period in 2014 was primarily attributable to:

- An approximately $2.2 million increase in professional fees and expenses, which consist primarily of legal, auditing, consulting and investor relations fees. Included in this expense is approximately $0.3 million in consulting expense for our pre-commercialization efforts.
- An approximately $0.9 million increase in payroll and related costs as administrative headcount increased from 15 to 18 to support corporate growth and to prepare for the filing of an NDA with the FDA and an MAA with the EMA, which were filed in July 2016 and June 2016, respectively.

- An approximately $0.6 million increase in facility and equipment costs. As described in Note 9—Commitments and Contingencies to our consolidated financial statements included in this report, we amended two of our office leases, which took effect April 2016.
- An approximately $0.7 million increase in other expenses primarily attributable to supporting our corporate growth.

Research and development expenses:

Research and development expenses (in thousands)	2016	2015	2014	Annual percentage change 2016/2015	Annual percentage change 2015/2014
Clinical trial expense	$ 79,934	$ 86,748	$ 63,856	-7.9%	35.8%
Consultants and contractors	13,243	11,203	5,262	18.2%	112.9%
Internal clinical development	26,795	22,447	15,397	19.4%	45.8%
Internal regulatory affairs and quality assurance	10,171	9,078	7,489	12.0%	21.2%
Internal chemical manufacturing	2,014	1,228	916	64.0%	34.1%
Employee stock-based compensation	90,641	77,768	29,997	16.6%	159.3%
	$ 222,798	$ 208,472	$ 122,917	6.9%	69.6%

Year Ended December 31, 2016 Compared to Year Ended December 31, 2015

For the year ended December 31, 2016, R&D expenses increased approximately $14.3 million compared to the same period in 2015. Approximately $12.8 million of this increase, or 89.5% of the total increase, is related to an increase in stock-based compensation expense, attributable to our increased headcount and additional incentive awards to existing employees. The remaining approximately $1.5 million increase in R&D expense for the year ended December 31, 2016 compared to the same period in 2015 was primarily attributable to:

- An approximately $6.8 million decrease in clinical trial expenses as a result of a decrease of approximately $14.3 million for CRO professional fees and pass-through costs offset by an approximately $7.5 million increase for clinical and pre-clinical services which includes drug manufacturing and supply as well as outside clinical services.
- An approximately $6.2 million increase for internal clinical development, internal regulatory affairs and quality assurance, and internal chemical manufacturing. Full-time R&D headcount at December 31, 2016 was 133 compared to 138 for the year ended December 31, 2015. We expect internal R&D expenses to continue at levels similar to 2016 as corporate focus shifts to commercial product launch.
- An approximately $2.0 million increase in consultants and contractors related expenses due to increased activity in our clinical trials and for activity to support the filing of an NDA with the FDA and MAA with the EMA during 2016.

Year Ended December 31, 2015 Compared to Year Ended December 31, 2014

For the year ended December 31, 2015, R&D expenses increased approximately $85.6 million compared to the same period in 2014. Approximately $47.8 million of this increase, or 55.8% of the total increase, is related to an increase in stock-based compensation expense, attributable to our increased headcount and additional incentive awards to existing employees. The remaining approximately $37.8 million increase in R&D expense for the year ended December 31, 2015 compared to the same period in 2014 was primarily attributable to:

- An approximately $22.9 million increase in clinical trial expenses as a result of an increase of approximately $9.4 million for CRO professional fees and pass-through costs and approximately $13.5 million for clinical and pre-clinical services which includes drug manufacturing and supply as well as outside clinical services.
- An approximately $9.0 million increase for internal clinical development, internal regulatory affairs and quality assurance, and internal chemical manufacturing. This increase represents an increase in full-time R&D headcount to 138 from 105 for the year ended December 31, 2015, compared to the same period in 2014.
- An approximately $5.9 million increase in consultants and contractors related expenses due to increased activity in our clinical trials and in preparation of filing an NDA with the FDA.

While expenditures on current and future clinical development programs, particularly our PB272 program, are expected to be substantial and to increase, th ey are subject to many uncertainties, including the results of clinical trials and whether we develop any of our drug candidates with a partner or independently. As a result of such uncertainties, we cannot predict with any significant degree of certainty the duration and completion costs of our research and development projects or whether, when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates. The duration and cost of clinical trials may vary significantly over the life of a project as a result of unanticipated events arising during clinical development and a variety of other factors, including:

- the number of trials and studies in a clinical program;
- the number of patients who participate in the trials;
- the number of sites included in the trials;
- the rates of patient recruitment and enrollment;
- the duration of patient treatment and follow-up;
- the costs of manufacturing our drug candidates; and
- the costs, requirements, timing of, and ability to secure regulatory approvals.

Interest income:

For the year ended December 31, 2016, we recognized approximately $1.0 million in interest income compared to approximately $1.0 million and $0.3 million of interest income for the years ended December 31, 2015 and 2014, respectively. The increase in interest income reflects excess cash invested in money market accounts, marketable securities and “high yield” savings accounts for a full year and cash invested from public offerings of our common stock completed in January 2015 and October 2016 (see Note 6 in the accompanying notes to consolidated financial statements).

Non-GAAP Financial Measures:

In addition to our operating results, as calculated in accordance with generally accepted accounting principles, or GAAP, we use certain non-GAAP financial measures when planning, monitoring, and evaluating our operational performance. The following table presents our net loss and net loss per share, as calculated in accordance with GAAP, as adjusted to remove the impact of employee stock-based compensation. For the three and twelve months ended December 31, 2016, stock-based compensation represented approximately 40.4% and 42.5% of our net loss, respectively. Although net loss is important to measure our financial performance, we currently place an emphasis on cash burn and, more specifically, cash used in operations. Because stock-based compensation appears in the GAAP net loss but is removed from net loss to arrive as cash used in operations on the statement of cash flows, due to its non-cash nature, we believe these non-GAAP measures enhance understanding of our financial performance, are more indicative of our operational performance and facilitate a better comparison among fiscal periods. These non-GAAP financial measures are not, and should not be viewed as, substitutes for GAAP reporting measures.

Reconciliation of GAAP Net Loss to Non-GAAP Adjuste d Net Loss and GAAP Net Loss Per Share to Non-GAAP Adjusted Net Loss Per Share
(in thousands except share and per share data)

	Years Ended December 31,			
	2016	2015	2014	
GAAP net loss	$ (276,011)	$ (239,284)	$ (141,965)	
Adjustments:				
Stock-based compensation:				
General and administrative	26,623	17,166	9,154	(1)
Research and development	90,641	77,768	29,997	(2)
Non-GAAP adjusted net loss	$ (158,747)	$ (144,350)	$ (102,814)	
GAAP net loss per share - basic and diluted	$ (8.29)	$ (7.45)	$ (4.73)	
Adjustment to net loss (as detailed above)	3.52	2.96	1.30	
Non-GAAP adjusted net loss per share	$ (4.77)	$ (4.49)	$ (3.43)	(3)

(1) To reflect a non-cash charge to operating expense for General and Administrative stock-based compensation.
(2) To reflect a non-cash charge to operating expense for Research and Development stock-based compensation.
(3) Non-GAAP adjusted net loss per share was calculated based on 33,295,114, 32,126,094 and 30,010,979 weighted average common shares outstanding for the years ended December 31, 2016, 2015 and 2014, respectively.

Liquidity and Capital Resources

Operating Activities

We reported net losses of approximately $276.0 million, $239.3 million and $142.0 million for the years ended December 31, 2016, 2015 and 2014, respectively. We also reported negative cash flows from operating activities of approximately $141.7 million, $154.5 million and $77.2 million for the years ended December 31, 2016, 2015 and 2014, respectively.

Net cash used in operating activities for the year ended December 31, 2016, includes a net loss of $276.0 million adjusted for non-cash items of approximately $117.3 million for stock-based compensation expense, build-out allowance of approximately $3.0 million, disposal of leasehold improvements of approximately $0.4 million and depreciation and amortization of property and equipment of approximately $1.1 million. Further changes in cash flows from operations include an increase in accounts payable and accrued expenses of approximately $5.0 million, a decrease in prepaid expenses and other of approximately $3.4 million and an increase in the accrued liability for deferred rent of approximately $4.1 million. This increase in accrued liability for deferred rent was due to the amendments to the leases for office space, which became effective in April 2016.

Net cash used in operating activities for the year ended December 31, 2015, includes a net loss of $239.3 million, adjusted for non-cash items of approximately $94.9 million for stock-based compensation expense, build-out allowance of $0.2 million and $0.8 million for depreciation and amortization of property and equipment. Further changes in cash flows from operations include a decrease in accounts payable and accrued expenses of approximately $12.0 million, a decrease of $1.8 million in Licensor receivables, and an increase in prepaid expenses and other assets of approximately $1.0 million. The decrease in accrued expenses reflects a payment of approximately $16.4 million for employee payroll taxes withheld related to the exercise of employee stock options during December 2014, paid in January 2015. The increase in prepaid expenses and other assets reflects up-front payments made to various CROs for company-initiated clinical trials, for various insurance policies and the comparator inventory.

Net cash used in operating activities for the year ended December 31, 2014, includes a net loss of $142.0 million adjusted for non-cash items of approximately $39.2 million for stock option expense, build-out allowance of $0.2 million and $0.6 million for depreciation and amortization of property and equipment. Further changes in cash flows from operations include an increase in accounts payable and accrued expenses of approximately $25.2 million, a decrease of $8.1 million in Licensor receivables, and an increase in prepaid expenses and other assets of approximately $8.6 million. The increase in both accounts payable and accrued expenses reflect an increase in clinical trial cost and an accrual of approximately $16.4 million for employee payroll taxes withheld related to the exercise of employee stock options during December 2014. The proceeds from the exercise of the stock options were primarily received in December 2014 while the payments for taxes withheld were made in January 2015. The increase in prepaid expenses and other assets reflects up-front payments made to various CROs for company-initiated clinical trials, various insurance policies and the comparator inventory.

Investing Activities

Net cash provided by investing activities was approximately $142.2 million for the year ended December 31, 2016. A significant portion represents cash provided by the sale and maturity of available-for-sale securities of approximately $231.3 million offset by cash used for the purchase of available-for-sale securities of approximately $81.8 million. Additionally, cash used included approximately $4.3 million used for the purchase of property and equipment and approximately $3.0 million for expenditures for leasehold improvements.

Net cash used in investing activities was approximately $85.9 million for the year ended December 31, 2015. A significant portion of this represents cash used for the purchase of available-for-sale securities of approximately $214.8 million offset by the sale and maturity of available-for-sale securities of $133.2 million. Additionally, approximately $3.1 million of net cash used in investing activities was transferred to restricted cash to secure a standby letter of credit for the additional office leases and approximately $1.2 million was used for leasehold improvements and the purchase of property and equipment to support corporate growth.

Net cash used in investing activities was approximately $63.3 million for the year ended December 31, 2014. A significant portion of this represents cash used for the purchase of available-for-sale securities of approximately $132.3 million offset by the sale and maturity of available-for-sale securities of $70.3 million. Additionally, approximately $1.3 million of cash used in investing activities was used for leasehold improvements and the purchase of property and equipment to support corporate growth.

Financing Activities

October 2016 Common Stock Offering. On October 19, 2016, we entered into an underwriting agreement in connection with the public offering, issuance and sale by us of 3,750,000 shares of our common stock at a public offering price of $40.00 per share, less underwriting discounts and commissions. Under the terms of the underwriting agreement, we also granted the underwriters an option exercisable for 30 days to purchase up to an additional 562,500 shares of our common stock at the public offering price, less underwriting discounts and commissions. On October 20, 2016, the underwriters exercised their option to purchase additional shares in full. We received net proceeds from the offering of approximately $161.9 million, after deducting underwriting discounts and commissions and estimated offering expenses.

In addition, during the year ended December 31, 2016, approximately $0.6 million was received for employee stock options exercised during 2016.

January 2015 Common Stock Offering . On January 27, 2015, we completed an underwritten public offering of 1,150,000 shares of our common stock (including an additional 150,000 shares of our common stock issued and sold pursuant to the underwriters' option to purchase additional shares) at a price of $190.00 per share, less the underwriting discount. The net proceeds received by us were approximately $205.1 million after deducting the underwriting discount and estimated offering expenses.

In addition, during the year ended December 31, 2015, $28.2 million was received for employee stock options exercised during 2015.

February 2014 Common Stock Offering . On February 14, 2014, we completed an underwritten public offering of 1,126,530 shares of our common stock (including an additional 146,938 shares of our common stock issued and sold pursuant to the underwriters' option to purchase additional shares) at a price of $122.50 per share, less the underwriting discount. The net proceeds received by us were approximately $129.4 million after deducting the underwriting discount and estimated offering expenses.

In addition, during the year ended December 31, 2014, $6.5 million was received for employee stock options exercised during 2014.

Current and Future Financing Needs

We have incurred negative cash flows from operations since we started our business, and we do not expect to achieve any product revenues for at least the next 6 to 12 months, if ever. We have spent, and expect to continue to spend, substantial amounts in connection with implementing our business strategy, including our planned product development efforts, our clinical trials, our R&D efforts and the commencement of commercialization efforts. Given the current and desired pace of clinical development of our product candidates, over the next 12 months we estimate that our R&D spending will be approximately $140 million to $150 million, excluding stock-based compensation.

Additionally, we expect increased G&A expenses as we continue to evaluate our options with regard to commercialization efforts.

We are currently exploring methods by which to commercialize our product candidates if approved by the FDA or EMA. These methods may require funding in addition to the cash and cash equivalents and marketable securities totaling approximately $229.4 million available at December 31, 2016. While our consolidated financial statements have been prepared on a going concern basis, we expect to continue incurring significant losses for the foreseeable future and will continue to remain dependent on our ability to obtain sufficient funding to sustain operation and successfully commercially launch neratinib if approved by the FDA or EMA. While we have been successful in raising financing in the past, there can be no assurance that we will be able to d o so in the future. Our ability to obtain funding may be adversely impacted by uncertain market conditions, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time. If the going concern assumption was not appropriate for the preparation of our consolidated financial statements, adjustment might be necessary to the consolidated financial statements.

In addition, we have based our estimate of the capital needs on assumptions that may prove to be wrong. Changes may occur that would consume our available capital faster than anticipated, including changes in and progress of our development activities, the impact of commercialization efforts, acquisitions of additional drug candidates and changes in regulation. Potential sources of financing include strategic relationships, public or private sales of equity or debt and other sources of funds. We may seek to access the public or private equity markets when conditions are favorable due to our long-term capital requirements. We do not have any committed sources of financing at this time, and it is uncertain whether additional funding will be available when we need it on terms that will be acceptable to us, or at all. If we raise funds by selling additional shares of common stock or other securities convertible into common stock, the ownership interests of our existing stockholders will be diluted. If we are not able to obtain financing when needed, we may be unable to carry out our business plan. As a result, we may have to significantly limit our operations, and our business, financial condition and results of operations would be materially harmed. In such an event, we will be required to undertake a thorough review of our programs, and the opportunities presented by such programs, and allocate our resources in the manner most prudent.

Going Concern

Our independent registered public accounting firm has issued a report on our audited consolidated financial statements for the year ended December 31, 2016 that included an explanatory paragraph referring to our significant operating losses and expressing substantial doubt in our ability to continue as a going concern. Our consolidated financial statements have been prepared on a going concern basis, which assumes the realization of assets and settlement of liabilities in the normal course of business. Our ability to continue as a going concern is dependent upon our ability to generate profitable operations in the future and/ or to obtain the necessary financing to meet our obligations and repay our liabilities arising from normal business operations when they become due. The outcome of these matters cannot be predicted with any certainty at this time and raise substantial doubt that we will be able to continue as a going concern. Our consolidated financial statements do not include any adjustments to the amount and classification of assets and liabilities that may be necessary should we be unable to continue as a going concern.

Off-Balance Sheet Arrangements

We do not have any “off-balance sheet arrangements,” as defined by the SEC regulations.

Contractual Obligations

Contractual obligations represent future cash commitments and liabilities under agreements with third parties, and exclude contingent liabilities for which we cannot reasonably predict future payment. Our contractual obligations result from property leases for office space. Although we do have obligations for CRO services, the table below excludes potential payments we may be required to make under our agreements with CROs because timing of payments and actual amounts paid under those agreements may be different depending on the timing of receipt of goods or services or changes to agreed-upon terms or amounts for some obligations, and those agreements are cancelable upon written notice by the Company and therefore, not long-term liabilities. The contracts also contain variable costs that are hard to predict as they are based on such things as patients enrolled and clinical trial sites, which can vary and therefore, are also not included in the table below. Additionally, the expected timing of payment of the obligations presented below is estimated based on current information.

The following table represents our contractual obligations as of December 31, 2016, aggregated by type (in thousands):

	Payments Due by Period				
Contractual Obligations	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating Lease Obligations	$ 41,370	$ 3,977	$ 8,315	$ 8,822	$ 20,256
Total	$ 41,370	$ 3,977	$ 8,315	$ 8,822	$ 20,256

Critical Accounting Policies

Our discussion and analysis of our consolidated financial condition and results of operations are based upon our consolidated financial statements, which have been prepared in conformity with accounting principles generally accepted in the United States of America, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, and expenses, and related disclosure of contingent assets and liabilities reported in our consolidated financial statements. The estimation process requires assumptions to be made about future events and conditions and, as a result, is inherently subjective and uncertain. Actual results could differ materially from our estimates.

The SEC defines critical accounting policies as those that are, in management's view, most important to the portrayal of our financial condition and results of operations and most demanding of our judgment. We consider the following policies to be critical to an understanding of our consolidated financial statements and the uncertainties associated with the complex judgments made by us that could impact our results of operations, financial position, and cash flows.

Property and Equipment:

Property and equipment are recorded at cost and depreciated over estimated useful lives ranging from three to five years using the straight-line method. Leasehold improvements are recorded at cost and amortized over the shorter of their useful lives or the term of the lease by use of the straight-line method. Maintenance and repair costs are charged to operations as incurred.

The Company assesses the impairment of long-lived assets, primarily property and equipment, whenever events or changes in business circumstances indicate that carrying amounts of the assets may not be fully recoverable. When such events occur, management determines whether there has been an impairment by comparing the asset's carrying value with its fair value, as measured by the anticipated undiscounted net cash flows of the asset. Should impairment exist, the asset is written down to its estimated fair value. The Company has not recognized any impairment losses through December 31, 2016.

Research and Development Expenses:

R&D expenses are charged to operations as incurred. The major components of R&D costs include clinical manufacturing costs; clinical trial expenses; consulting and other third-party costs; salaries and employee benefits; stock-based compensation expense; supplies and materials; and allocations of various overhead costs. Clinical trial expenses include, but are not limited to, investigator fees, site costs, comparator drug costs, and CRO costs. In the normal course of business, we contract with third parties to perform various clinical trial activities in the ongoing development of potential products. The financial terms of these agreements are subject to negotiation and variations from contract to contract and may result in uneven payment flows. Payments under the contracts depend on factors such as the achievement of certain events, the successful enrollment of patients and the completion of portions of the clinical trial or similar conditions. Our cost accruals for clinical trials are based on estimates of the services received and efforts expended pursuant to contracts with numerous clinical trial sites, cooperative groups and CROs. The objective of our accrual policy is to match the recording of expenses in our consolidated financial statements to the actual services received and efforts expended. As actual costs become known, we adjust our accruals in that period.

In instances where we enter into agreements with third parties for clinical trials and other consulting activities, upfront amounts are recorded as prepaid expenses and expensed as services are performed or as the underlying goods are delivered. If we do not expect the services to be rendered or goods to be delivered, any remaining capitalized amounts for non-refundable upfront payments are charged to expense immediately. Amounts due under such arrangements may be either fixed fee or fee for service, and may include upfront payments, monthly payments and payments upon the completion of milestones or receipt of deliverables.

Costs related to the acquisition of technology rights and patents for which development work is still in process are charged to operations as incurred and considered a component of R&D costs.

Research and Development Reimbursement:

The licensing agreement set a "cap" on the amount of external expenses we would incur, beginning January 1, 2012, in completing the clinical trials transferred from the Licensor to the Company. The license agreement originally stipulated that the Licensor would be responsible for all external expenses associated with the transferred clinical trials and that we would invoice for such costs on a quarterly basis. The Licensor had 60 days to review the invoice and supporting documentation. All amounts reimbursed from the Licensor represent charges for services provided by third parties and not by us. Accordingly, we have elected to treat the reimbursed costs as a "pass-through" expense billable to the Licensor and as an offset to our R&D expenses. Therefore, our R&D expenses are recorded net of any excess cap costs billed to the Licensor. We recognized approximately $16.4 million of excess cap cost billings in the year ended December 31, 2013.

The license agreement was amended in July 2014 and made the Company solely responsible for the expenses incurred or accrued in conducting the ongoing legacy clinical trials after December 31, 2013. Pursuant to the amen dment to the original license agreement, no reductions in the expenses related to the licensor legacy clinical trials that were in excess of the cap on such expenses set forth in the license agreement were recorded in the years ended December 31, 2016, 201 5 and 2014.

Stock-Based Compensation:

Stock option awards:

Accounting Standards Codification 718, *Compensation-Stock Compensation* , or ASC 718, requires the fair value of all share-based payments to employees, including grants of stock options, to be recognized in the statement of operations over the requisite service period. Under ASC 718, employee option grants are generally valued at the grant date and those valuations do not change once they have been established. The determination of the fair value using the Black-Scholes Option Pricing Method is affected by our stock price as well as a number of complex and subjective variables, including expected stock price volatility, risk-free interest rate, expected dividends and projected employee stock option exercise behaviors. As allowed by ASC 718 for companies with a short period of publicly traded stock history, our estimate of expected volatility is based on the average expected volatilities of a sampling of six companies with similar attributes to us, including industry, stage of life cycle, size and financial leverage. The six companies are reviewed quarterly as volatility has the greatest impact on the calculation. The risk-free rate for periods within the contractual life of the option is based on the U.S. Treasury yield curve in effect at the time of grant valuation. Option forfeitures are calculated when the option is granted to reduce the option expense to be recognized over the life of the award and updated upon receipt of further information as to the amount of options expected to be forfeited. The option expense is “trued-up” upon the actual forfeiture of a stock option grant. Due to our limited history, we use the simplified method to determine the expected life of the option grants.

Performance share awards:

The performance shares are valued on the grant date and the fair value of the performance award is equal to the market price of the Company’s common stock on the grant date. The performance share expense is recognized based on the Company’s estimate of a range of probabilities that the Company’s closing common stock price will be lower or higher on the vesting dates than the Company’s common stock price on the grant date. Based on the range of probabilities, the expense is calculated and recognized over the three-year vesting period.

Restricted stock units:

The restricted stock units, or RSUs, are valued on the grant date and the fair value of the RSUs is equal to the market price of the Company’s common stock on the grant date. The RSU expense is recognized over the requisite service period. When the requisite service period begins prior to the grant date (because the service inception date occurs prior to the grant date), the Company is required to begin recognizing compensation cost before there is a measurement date (i.e., the grant date). The service inception date is the beginning of the requisite service period. If the service inception date precedes the grant date, accrual of compensation cost for periods before the grant date shall be based on the fair value of the award at the reporting date. In the period in which the grant date occurs, cumulative compensation cost shall be adjusted to reflect the cumulative effect of measuring compensation cost based on fair value at the grant date rather than the fair value previously used at the service inception date (or any subsequent reporting date).

Warrants:

Warrants granted to employees are normally valued at the fair value of the instrument on the grant date and are recognized in the statement of operations over the requisite service period. When the requisite service period precedes the grant date and a market condition exists in the warrant, the Company values the warrant using the Monte Carlo Simulation Method. When the terms of the warrant become fixed, the Company values the warrant using the Black-Scholes Option Pricing Method. As allowed by ASC 718 for companies with a short period of publicly traded stock history, the Company’s estimate of expected volatility is based on the average volatilities of a sampling of eight to nine companies with similar attributes to the Company, including industry, stage of life cycle, size and financial leverage. The risk-free rate for periods within the contractual life of the warrant is based on the U.S. Treasury yield curve in effect at the time of grant valuation. In determining the value, until the terms are fixed the Company factors in the probability of the market condition occurring and several possible scenarios. When the requisite service period precedes the grant date and is deemed to be complete, the Company records the fair value of the warrant at the time of issuance as an equity stock-based compensation transaction. The warrant is revalued each reporting period up to the grant date when the final fair value of the warrant is established and recorded. The grant date is determined when all pertinent information, such as exercise price and quantity are known.

Recently Issued Accounting Standards

In January 2016, the Financial Accounting Standards Board, or FASB, issued ASU No. 2016-01, *Recognition and Measurement of Financial Assets and Financial Liabilities* . The amendments in ASU 2016-01 address certain aspects of recognition, measurement, presentation and disclosure of financial instruments. ASU 2016-01 will be effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years. Early adoption of some of the amendments included in ASU 2016-01 for

financial statements of fiscal years or interim p eriods that have not yet been issued is permitted as of the beginning of the fiscal year of adoption. The Company is currently evaluating the effect that the adoption of ASU 2016-01 will have on its consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* . The amendments in ASU 2016-02 will require organizations that lease assets, with lease terms of more than 12 months, to recognize on the balance sheet the assets and liabilities for the rights and obligations created by those leases. Consistent with current U.S. GAAP, the recognition, measurement, and presentation of expenses and cash flows arising from a lease by a lessee primarily will depend on its classification as a finance or operating lease. However, unlike current U.S. GAAP which requires only capital leases to be recognized on the balance sheet, ASU No. 2016-02 will require both types of leases to be recognized on the balance sheet. ASU 2016-02 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years. Early adoption is permitted. The Company is currently evaluating the effect that the adoption of ASU 2016-02 will have on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-06, *Derivatives and Hedging* (Topic 815): *Contingent Put and Call Options in Debt Instruments* . ASU 2016-06 amends FASB ASC 815-15 to clarify what steps are required when assessing whether the economic characteristics and risks of call (put) options are clearly and closely related to the economic characteristics and risks of their debt hosts, which is one of the criteria for bifurcating an embedded derivative. ASU 2016-06 will be effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years. An entity should apply the amendments in ASU No. 2016-06 on a modified retrospective basis to existing debt instruments as of the beginning of the fiscal year for which the amendments are effective. Early adoption is permitted, including adoption in an interim period. The Company is currently evaluating the effect that the adoption of ASU 2016-06 will have on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation – Stock Compensation* (Topic 718). ASU 2016-09 will require organizations to recognize all income tax effects of awards in the statement of operations when the awards vest or are settled. ASU 2016-09 will also allow organizations to repurchase more shares from employees than they could previously purchase for tax withholding purposes without triggering liability accounting and to make a policy election to account for forfeitures as they occur. ASU 2016-09 will be effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. Early adoption is permitted in any interim or annual period. The Company is currently evaluating the effect that the adoption of ASU 2016-09 will have on its consolidated financial statements.

In April 2016, the FASB issued ASU No. 2016-10, *Revenue from Contracts with Customers* (Topic 606). ASU 2016-10 amends ASC 606, *Revenue from Contracts with Customers* , to clarify two aspects of ASC 606, identifying performance obligations and the licensing implementation guidance, while retaining the related principles of those areas. The amendments in ASU 2016-10 do not change the core principle of the guidance in ASC 606. The amendments in ASU No. 2016-10 affect the guidance in ASU 2014-09, Revenue from Contracts with Customers (Topic 606), which is not yet effective. The effective date and transition requirements for the amendments in ASU No. 2016-10 are the same as the effective date and transition requirements in ASC 606 and any other Topic amended by ASU 2014-09. ASU 2015-14, *Revenue from Contracts with Customers* (Topic 606): *Deferral of the Effective Date* , defers the effective date of ASU 2014-09 by one year to annual reporting periods beginning after December 15, 2017, including interim reporting periods within that reporting period. The Company is currently evaluating the effect that the adoption of ASU 2016-10 will have on its consolidated financial statements.

In May 2016, the FASB issued ASU No. 2016-12, *Revenue from Contracts with Customers* (Topic 606). ASU 2016-12 amends ASC 606 to address certain issues in the guidance on assessing collectability, presentation of sales taxes, noncash consideration, and completed contracts and contract modifications at transition. The amendments in ASU 2016-12 do not change the core principle of the guidance in ASC 606. The amendments in ASU No. 2016-12 affect the guidance in ASU 2014-09, *Revenue from Contracts with Customers* (Topic 606), which is not yet effective. The effective date and transition requirements for the amendments in ASU No. 2016-12 are the same as the effective date and transition requirements in ASC 606 and any other Topic amended by ASU 2014-09. ASU 2015-14, *Revenue from Contracts with Customers* (Topic 606): *Deferral of the Effective Date* , defers the effective date of ASU 2014-09 by one year to annual reporting periods beginning after December 15, 2017, including interim reporting periods within that reporting period. The Company is currently evaluating the effect that the adoption of ASU 2016-12 will have on its consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows* (Topic 230) *: Classification of Certain Cash Receipts and Cash Payments* (a consensus of the Emerging Issues Task Force), which addresses the diversity in practice in how certain cash receipts and cash payments are presented and classified in the statement of cash flows. This update addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. ASU 2016-15 will be effective for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. The Company is currently evaluating the impact of adopting ASU 2016-15 on its consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows* (Topic 230): *Restricted Cash* that changes the presentation of restricted cash and cash equivalents on the statement of cash flows. Restricted cash and restricted cash equivalents will be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This amendment is effective for the Company in th e fiscal year beginning after December 15, 2017, but early adoption is permissible. The Company is currently evaluating the effect that the adoption of ASU 2016-18 will have on its consolidated financial statements.

I TEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

The primary objective of our investing activities is to preserve principal while maximizing the income we receive from our investments without significantly increasing the risk of loss. Some of the investable securities permitted under our cash management policy may be subject to market risk for changes in interest rates. To mitigate this risk, we maintain a portfolio of cash equivalents and available-for-sale investments in a variety of securities, which may include investment grade commercial paper, money market funds, government debt issued by the United States of America, state debt, certificates of deposit and investment grade corporate debt. Presently, we are exposed to minimal market risks associated with interest rate changes because of the relatively short maturities of our investments and we do not expect interest rate fluctuations to materially affect the aggregate value of our financial instruments. We manage our sensitivity to these risks by maintaining investments-grade short-term investments. Our cash management policy does not allow us to purchase or hold derivative or commodity instruments or other financial instruments for trading purposes. Additionally, our policy stipulates that we periodically monitor our investments for adverse material holdings related to the underlying financial solvency of the issuer. As of December 31, 2016, our investments consisted primarily of commercial paper and corporate obligations. Our results of operations and financial condition would not be significantly impacted by either a 10% increase or 10% decrease in interest rates due mainly to the short-term nature of our investment portfolio. We have not used derivative financial instruments in our investment portfolio. Additionally, we do not invest in foreign currencies or other foreign investments.

I TEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

All financial statements and supplementary data required by this Item are listed in Part IV, Item 15 of this Annual Report and are presented beginning on Page F-1.

I TEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

I TEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our reports under the Exchange Act, is recorded, processed, summarized and reported within the timelines specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Senior Vice President, Finance and Administration and Treasurer, as appropriate, to allow timely decisions regarding required disclosures. In designing and evaluating the disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can only provide reasonable assurance of achieving the desired control objectives and in reaching a reasonable level of assurance, management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Senior Vice President, Finance and Administration and Treasurer, we have evaluated the effectiveness of our disclosure controls and procedures (as defined under Exchange Act Rule 13a-15(e)), as of December 31, 2016. Based on that evaluation, our Chief Executive Officer and Senior Vice President, Finance and Administration and Treasurer have concluded that these disclosure controls and procedures were effective as of December 31, 2016.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting that occurred during the fourth quarter ended December 31, 2016, that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Senior Vice President, Finance and Administration and Treasurer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2016. Management based its assessment on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control—Integrated Framework - 2013* (COSO 2013 framework). Based on this evaluation and criteria, our management concluded that as of December 31, 2016, our internal control over financial reporting was effective at the reasonable assurance level.

Our internal control over financial reporting as of December 31, 2016 has been audited by PKF, Certified Public Accountants, A Professional Corporation, our independent registered public accounting firm, as stated in their report, which expresses an unqualified opinion on the effectiveness of the Company's internal control over financial reporting as of December 31, 2016.

I TEM 9B. OTHER INFORMATION

Not applicable.

Part III

I TEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item will be included in our 2017 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

I TEM 11. EXECUTIVE COMPENSATION

The information required by this Item will be included in our 2017 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

I TEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item will be included in our 2017 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

I TEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item will be included in our 2017 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

I TEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by this Item will be included in our 2017 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

Part IV

I TEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

Reference is made to the Index to Consolidated Financial Statements beginning on Page F-1 hereof.

Consolidated Financial Statement Schedules

(a) Documents Filed as Part of Report

(1) Consolidated Financial Statements

(2) Consolidated Financial Statement Schedules

Consolidated Financial Statement Schedules have been omitted because they are either not required or not applicable, or because the information required to be presented is included in the consolidated financial statements or the notes thereto included in this Annual Report.

(3) Exhibits

The exhibits listed on the accompanying Exhibit Index are filed or incorporated by reference as part of this Annual Report and such Exhibit Index is incorporated by reference herein.

S ignatures

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on March 1, 2017.

PUMA BIOTECHNOLOGY, INC.

By: /s/ Alan H. Auerbach
Alan H. Auerbach
President & Chief Executive Officer
(Principal Executive Officer)

KNOWN BY ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Alan H. Auerbach and Charles R. Eyler, or either of them, as his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K and any documents related to this report and filed pursuant to the Securities Exchange Act of 1934, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their substitute or substitutes may lawfully do or cause to be done by virtue hereof. This power of attorney shall be governed by and construed with the laws of the State of Delaware and applicable federal securities laws.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Alan H. Auerbach Alan H. Auerbach	Chairman of the Board of Directors, President and Chief Executive Officer (Principal Executive Officer)	March 1, 2017
/s/ Charles R. Eyler Charles R. Eyler	Senior Vice President, Finance and Administration and Treasurer (Principal Financial Officer and Principal Accounting Officer)	March 1, 2017
/s/ Jay M. Moyes Jay M. Moyes	Director	March 1, 2017
/s/ Adrian M. Senderowicz Adrian M. Senderowicz	Director	March 1, 2017
/s/ Troy E. Wilson Troy E. Wilson	Director	March 1, 2017
/s/ Frank Zavrl Frank Zavrl	Director	March 1, 2017

EXHIBIT INDEX

Exhibit No.		Incorporation by Reference		
		Form	Exhibit	Filing Date
2.1	Agreement and Plan of Merger, dated September 29, 2011, by and among Innovative Acquisitions Corp., IAC Merger Corporation, a Delaware corporation and wholly-owned subsidiary of the Company, and Puma Biotechnology, Inc., a Delaware corporation	8-K	2.1	10/4/2011
3.1	Certificate of Merger relating to the merger of IAC Merger Corporation with and into Puma Biotechnology, Inc., filed with the Secretary of State of Delaware on October 4, 2011	8-K	3.1	10/11/2011
3.2	Certificate of Ownership and Merger relating to the merger of Puma Biotechnology, Inc. with and into Innovative Acquisitions Corp., filed with the Secretary of State of the State of Delaware on October 4, 2011	8-K	3.2	10/11/2011
3.3	Second Amended and Restated Certificate of Incorporation, as filed with the Secretary of State of the State of Delaware on June 14, 2016	8-K	3.1	6/15/2016
3.4	Amended and Restated Bylaws of Puma Biotechnology, Inc.	K	3.1	2/16/2016
4.1	Form of Common Stock Certificate	S-1/A	4.1	2/1/2012
4.2#	Warrant to Purchase Shares of Common Stock of Puma Biotechnology, Inc., dated October 4, 2011, issued to Alan H. Auerbach	8-K	4.2	10/11/2011
10.1(a)*	License Agreement, dated August 18, 2011, by and between the Company, as successor to Puma Biotechnology, Inc., and Pfizer Inc.	8-K/A	10.1	12/16/2011
10.1(b)*	Amendment No. 1 to License Agreement dated July 18, 2014, between the Company and Pfizer, Inc.	10-Q	10.1	11/10/2014
10.2(a)#	Puma Biotechnology, Inc. 2011 Incentive Award Plan	8-K	10.4	10/11/2011
10.2(b)#	First Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan	DEF 14A	Appendix A	6/4/2014
10.2(c)#	Second Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan	10-Q	10.1	8/10/2015
10.2(d)#	Form of Stock Option Grant Notice and Stock Option Agreement, issued pursuant to the 2011 Incentive Award Plan	10-K	10.5	3/29/2012
10.2(e)#	Form of Chief Executive Officer Stock Option Grant Notice and Stock Option Agreement, issued pursuant to the 2011 Incentive Award Plan	10-K	10.6	3/29/2012
10.2(f)#	Form of Performance Share Award Agreement, issued pursuant to the 2011 Incentive Award Plan	10-K	10.2(d)	3/3/2014
10.2(g)#	Form of Restricted Stock Unit Award Agreement, issued pursuant to the 2011 Incentive Award Plan	8-K	10.1	10/17/2016
10.3(a)	Registration Rights Agreement, dated October 4, 2011, by and among Puma, the investors listed on Exhibit A attached thereto and the Company	8-K/A	10.5	12/16/2011
10.3(b)	Amendment No. 1 to Registration Rights Agreement	8-K	10.2	11/23/2011
10.4#	Letter Agreement, dated October 21, 2011, between the Company and Charles Eyler	8-K	10.2	10/27/2011

Exhibit No.		Incorporation by Reference		
		Form	Exhibit	Filing Date
10.5(a)	Office Lease by and between the Company and CA – 10880 Wilshire Limited Partnership, executed on December 7, 2011	8-K	10.1	12/13/2011
10.5(b)	First Amendment to the Office Lease, dated as of November 28, 2012, by and between the Company and CA – 10880 Wilshire Limited Partnership	10-K	10.13(B)	4/1/2013
10.5(c)	Second Amendment to the Office Lease, dated as of December 3, 2013, by and between the Company and CA – 10880 Wilshire Limited Partnership	10-K	10.6(c)	3/3/2014
10.5(d)	Third Amendment to the Office Lease, dated as of March 18, 2014, by and between the Company and CA – 10880 Wilshire Limited Partnership	10-K	10.5(d)	3/2/2015
10.5(e)	Fourth Amendment to the Office Lease, dated as of July 31, 2015, by and between the Company and CA – 10880 Wilshire Limited Partnership	10-Q	10.1	11/9/2015
10.6#	Employment Agreement, dated January 19, 2012, by and between the Company and Alan H. Auerbach	8-K	10.1	1/24/2012
10.7(a)	Office Lease by and between DWF III Gateway, LLC and the Company, executed June 7, 2012	8-K	10.1	6/13/2012
10.7(b)	First Amendment to Lease, dated as of May 19, 2014, by and between DWF III Gateway, LLC and Puma Biotechnology, Inc.	8-K	10.1	5/23/2014
10.7(c)	Second Amendment to Lease, dated as of June 10, 2014, by and between DWF III Gateway, LLC and Puma Biotechnology, Inc.	10-Q	10.2	8/10/2015
10.7(d)	Third Amendment to Lease, dated as of July 21, 2015, by and between PR 707 Gateway, LLC (as sucessor in interest to DWF III Gateway, LLC) and the Company	10-Q	10.2	11/9/2015
10.8#	Letter Agreement, dated May 2, 2012, between the Company and Richard P. Bryce	8-K	10.17	6/26/2012
10.9#	Form of Indemnification Agreement	S-1/A	10.11	10/15/2012
10.10#	Non-Employee Director Compensation Program	10-K	10.10	2/29/2016
10.11#	Letter Agreement, dated August 21, 2015, between the Company and Steven Lo	10-Q	10.3	11/9/2015
10.12#	Letter Agreement, dated April 15, 2016, between the Company and Richard Phillips	10-Q	10.1	8/9/2016
10.13#	Amendment to Stock Option Grant Notice and Stock Option Agreement, dated August 1, 2016, between the Company and Richard Phillips	10-Q	10.1	11/9/2016
10.14#	Letter Agreement, dated May 24, 2016, between the Company and Richard Charnas	10-Q	10.2	8/9/2016
21.1+	Subsidiaries			
23.1+	Consent of Independent Registered Public Accounting Firm			
24.1+	Power of Attorney (included on signature page)			
31.1+	Certification of Principal Executive Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002			
31.2+	Certification of Principal Financial Officer, as required by Section 302 of the Sarbanes-Oxley Act of 2002			

Exhibit No.		Incorporation by Reference		
		Form	Exhibit	Filing Date
32.1++	Certification of Principal Executive Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002			
32.2++	Certification of Principal Financial Officer, as required by Section 906 of the Sarbanes-Oxley Act of 2002			
101.INS+	XBRL Instance Document			
101.SCH+	XBRL Taxonomy Extension Schema Document			
101.CAL+	XBRL Taxonomy Extension Calculation Linkbase Document			
101.DEF+	XBRL Taxonomy Extension Definition Linkbase Document			
101.LAB+	XBRL Taxonomy Extension Label Linkbase Document			
101.PRE+	XBRL Taxonomy Extension Linkbase Document			

\+ File herewith.

++ Furnished herewith.

* Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment pursuant to Rule 24b-2 under the Securities Exchange Act of 1934.

\# Management contract or compensatory plan or arrangement.

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

R EPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Puma Biotechnology, Inc. and Subsidiary

We have audited the accompanying consolidated balance sheets of Puma Biotechnology, Inc. and Subsidiary (the "Company") as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years ended 2016, 2015 and 2014. We also have audited Puma Biotechnology, Inc.'s internal control over financial reporting as of December 31, 2016, based on criteria established in *Internal Control—Integrated Framework - 2013* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Puma Biotechnology Inc.'s management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on these consolidated financial statements and an opinion on the Company's internal control over financial reporting based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the consolidated financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the consolidated financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with accounting principles generally accepted in the United States of America, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the consolidated financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Puma Biotechnology, Inc. and Subsidiary as of December 31, 2016 and 2015, and the results of its operations, comprehensive loss, changes in stockholders' equity and its cash flows for each of the three years ended 2016, 2015, and 2014, in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, Puma Biotechnology, Inc. and Subsidiary maintained, in all material respects, effective internal control over financial reporting as of December 31, 2016, based on criteria established in *Internal Control—Integrated Framework - 2013* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company's significant operating losses raise substantial doubt about its ability to continue as a going concern. Management's plans regarding those matters also are described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. Our opinion is not modified with respect to that matter.

/s/ PKF
PKF
Certified Public Accountants
A Professional Corporation

San Diego, California
March 1, 2017

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	December 31, 2016	December 31, 2015
ASSETS		
Current assets:		
Cash and cash equivalents	$ 194,494	$ 31,569
Marketable securities	34,982	184,320
Prepaid expenses and other, current	6,998	7,660
Total current assets	236,474	223,549
Property and equipment, net	5,153	2,383
Prepaid expenses and other, long-term	6,846	9,597
Restricted cash	4,317	4,313
Total assets	$ 252,790	$ 239,842
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 20,035	$ 17,803
Accrued expenses	17,426	14,639
Total current liabilities	37,461	32,442
Deferred rent	5,505	1,393
Total liabilities	42,966	33,835
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Common stock - $.0001 par value; 100,000,000 shares authorized; 36,826,010 issued and outstanding at December 31, 2016, and 32,466,842 issued and outstanding at December 31, 2015	4	3
Additional paid-in capital	1,006,344	726,651
Accumulated other comprehensive loss	(13)	(147)
Accumulated deficit	(796,511)	(520,500)
Total stockholders' equity	209,824	206,007
Total liabilities and stockholders' equity	$ 252,790	$ 239,842

See Accompanying Notes to the Consolidated Financial Statements

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands except per share data)

	Years Ended December 31,		
	2016	**2015**	**2014**
Operating expenses:			
General and administrative	$ 53,798	$ 31,808	$ 19,358
Research and development	222,798	208,472	122,917
Totals	276,596	240,280	142,275
Loss from operations	(276,596)	(240,280)	(142,275)
Other income (expenses):			
Interest income	958	971	324
Other income (expense)	(373)	25	(14)
Totals	585	996	310
Net loss	$ (276,011)	$ (239,284)	$ (141,965)
Net loss applicable to common stock	$ (276,011)	$ (239,284)	$ (141,965)
Net loss per common share—basic and diluted	$ (8.29)	$ (7.45)	$ (4.73)
Weighted-average common shares outstanding—basic and diluted	33,295,114	32,126,094	30,010,979

See Accompanying Notes to the Consolidated Financial Statements

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)

	Years Ended December 31,		
	2016	2015	2014
Net loss	$ (276,011)	$ (239,284)	$ (141,965)
Other comprehensive income (loss)			
Unrealized gain (loss) on available-for-sale securities	134	(52)	(98)
Comprehensive loss	$ (275,877)	$ (239,336)	$ (142,063)

See Accompanying Notes to the Consolidated Financial Statements

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands except share data)

	Common Stock		Additional Paid-in Capital	Receivables from the Exercise of Options	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total
	Shares	Amount					
Balance at December 31, 2013	28,991,289	3	223,232	—	3	(139,251)	83,987
Stock option compensation	—	—	39,151	—	—	—	39,151
Exercises of stock options	430,490	—	7,368	(835)	—	—	6,533
Issuance of shares of common stock through equity placement at $122.50 per share, net of issuance costs	1,126,530	—	129,440	—	—	—	129,440
Unrealized loss on available for sale securities	—	—	—	—	(98)	—	(98)
Net loss	—	—	—	—	—	(141,965)	(141,965)
Balance at December 31, 2014	30,548,309	3	399,191	(835)	(95)	(281,216)	117,048
Stock-based compensation	—	—	94,934	—	—	—	94,934
Exercises of stock options	757,038	—	27,393	835	—	—	28,228
Issuance of performance shares	11,495	—	—	—	—	—	—
Issuance of shares of common stock through equity placement at $190.00 per share, net of issuance costs	1,150,000	—	205,133	—	—	—	205,133
Unrealized gain on available for sale securities	—	—	—	—	(52)	—	(52)
Net loss	—	—	—	—	—	(239,284)	(239,284)
Balance at December 31, 2015	32,466,842	3	726,651	—	(147)	(520,500)	206,007
Stock-based compensation	—	—	117,264	—	—	—	117,264
Exercises of stock options	46,668	—	576	—	—	—	576
Unrealized gain on available-for-sale securities	—	—	—	—	134	—	134
Issuance of shares of common stock through equity placement at $40.00 per share, net of issuance costs	4,312,500	1	161,853	—	—	—	161,854
Net loss	—	—	—	—	—	(276,011)	(276,011)
Balance at December 31, 2016	36,826,010	$ 4	$ 1,006,344	$ —	$ (13)	$ (796,511)	$ 209,824

See Accompanying Notes to the Consolidated Financial Statements

PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARY
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Years Ended December 31,		
	2016	2015	2014
Operating activities:			
Net loss	$ (276,011)	$ (239,284)	$ (141,965)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	1,149	776	627
Build-out allowance received from landlord	2,997	179	192
Disposal of leasehold improvements	368	—	—
Stock-based compensation expense	117,264	94,934	39,151
Changes in operating assets and liabilities:			
Licensor receivable	—	1,760	8,053
Prepaid expenses and other	3,413	(958)	(8,584)
Accounts payable	2,231	2,806	4,305
Accrued expenses	2,787	(14,805)	20,865
Accrual of deferred rent	4,112	124	153
Net cash used in operating activities	(141,690)	(154,468)	(77,203)
Investing activities:			
Purchase of property and equipment	(4,287)	(1,002)	(1,100)
Expenditures for leasehold improvements	(2,997)	(179)	(192)
Restricted cash	(4)	(3,098)	(1)
Purchase of available-for-sale securities	(81,794)	(214,806)	(132,259)
Sale/maturity of available-for-sale securities	231,267	133,222	70,277
Net cash provided by (used in) investing activities	142,185	(85,863)	(63,275)
Financing activities:			
Net proceeds from issuance of common stock	161,854	205,133	129,440
Net proceeds from exercise of options	576	28,228	6,533
Net cash provided by financing activities	162,430	233,361	135,973
Net increase (decrease) in cash and cash equivalents	162,925	(6,970)	(4,505)
Cash and cash equivalents, beginning of year	31,569	38,539	43,044
Cash and cash equivalents, end of year	$ 194,494	$ 31,569	$ 38,539
Supplemental disclosures of non-cash investing and financing activities:			
Receivables from the exercise of options	$ —	$ —	$ 835

See Accompanying Notes to the Consolidated Financial Statements

Note 1—Business and Basis of Presentation:

Business:

Puma Biotechnology, Inc., or Puma, is a biopharmaceutical company based in Los Angeles, California. References in these Notes to Consolidated Financial Statements to the "Company" refer to Puma Biotechnology, Inc., a private Delaware company formed on September 15, 2010, or Private Puma, for periods prior to the merger of Private Puma with Public Puma (as defined below), which took place on October 4, 2011, or the Merger, and Puma Biotechnology, Inc., a Delaware company formed on April 27, 2007, and formerly known as Innovative Acquisitions Corp., or Public Puma, for periods following the Merger. The Company is a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. The Company in-licenses the global development and commercialization rights to three drug candidates—PB272 (neratinib (oral)), PB272 (neratinib (intravenous)) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor, or TKI, that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Currently, the Company is primarily focused on the development of the oral version of neratinib, and its most advanced drug candidates are directed at the treatment of HER2-positive breast cancer. The Company believes neratinib has clinical application in the treatment of several other cancers as well, including non-small cell lung cancer and other tumor types that over-express or have a mutation in HER2.

In November 2012, the Company established and incorporated Puma Biotechnology Ltd., a wholly owned subsidiary, for the sole purpose of serving as Puma's legal representative in the United Kingdom and the European Union in connection with Puma's clinical trial activity in those countries.

Basis of Presentation:

The Company is focused on developing neratinib for the treatment of patients with human epidermal growth factor receptor type 2, or 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. The Company has reported a net loss of approximately $276.0 million and negative cash flows from operations of approximately $141.7 million for the year ended December 31, 2016. Management believes that the Company will continue to incur net losses and negative net cash flows from operating activities through the drug development process and into the early commercialization stage.

The Company has incurred significant operating losses since its inception, which raises substantial doubt about its ability to continue as a going concern. The Company has not yet launched its first commercial product and is currently exploring methods by which to commercialize its product candidates if approved by the FDA or EMA. These methods may require funding in addition to the cash and cash equivalents and marketable securities totaling approximately $229.4 million available at December 31, 2016. While the consolidated financial statements have been prepared on a going concern basis, the Company continues to remain dependent on its ability to obtain sufficient funding to sustain operation and successfully commercially launch neratinib if approved by the FDA or EMA. While the Company has been successful in raising financing in the past, there can be no assurance that it will be able to do so in the future. The Company's ability to obtain funding may be adversely impacted by uncertain market conditions, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time. If the going concern assumption was not appropriate for the preparation of the consolidated financial statements, adjustment might be necessary to the consolidated financial statements.

The Company's continued operations will depend on its ability to raise funds through various potential sources, such as equity and debt financing. Through December 31, 2016, the Company's financing was primarily through public offerings of Company common stock and private equity placements. The Company sold additional shares of its common stock through an underwritten public offering in October 2016 (see Note 6). As a result, the Company received net proceeds of approximately $161.9 million. The Company may need additional financing until it can achieve profitability, if ever. There can be no assurance that additional capital will be available on favorable terms or at all or that any additional capital that the Company is able to obtain will be sufficient to meet its needs. If it is unable to raise additional capital, the Company could likely be forced to curtail desired development activities, which will delay the development of its product candidates.

Note 2—Significant Accounting Poli cies:

The significant accounting policies followed in the preparation of these consolidated financial statements are as follows:

Use of Estimates:

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America, or GAAP, requires management to make estimates and assumptions that affect reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the balance sheet and reported amounts of expenses for the period presented. Accordingly, actual results could differ from those estimates. Significant estimates include accrued expenses for the cost of services provided by consultants who manage clinical trials and conduct research and clinical trials on behalf of the Company that are billed on a delayed basis. As the actual costs become known, the Company adjusts its estimated cost in that period. The value of stock-based compensation includes estimates based on future events, which are difficult to predict. It is at least reasonably possible that a change in the estimates used to record accrued expenses and to value stock-based compensation will occur in the near term.

Principles of Consolidation:

The Consolidated Financial Statements include the accounts of the Company and its wholly owned subsidiary. All significant intercompany balances and transactions have been eliminated in consolidation.

Cash and Cash Equivalents:

The Company considers all highly liquid investments with original maturities of three months or less to be cash equivalents. Cash equivalents are carried at cost, which approximates fair value.

Licensor Receivable:

Pfizer, Inc., or the Licensor, receivable represents the remaining external “out of pocket” clinical trial costs in excess of an agreed upon “cap” for clinical trials that were ongoing at the time the licensing agreement with the Licensor was reached. In July 2014, the license agreement was amended to make the Company solely responsible for the expenses incurred or accrued in conducting the ongoing legacy clinical trials after December 31, 2013, and to fix the future royalty rate that must be paid to the Licensor upon commercialization in the low to mid-teens.

Investment Securities:

The Company classifies all investment securities (short term and long term) as available-for-sale, as the sale of such securities may be required prior to maturity to implement management’s strategies. These securities are carried at fair value, with the unrealized gains and losses, reported as a component of accumulated other comprehensive loss in stockholders’ equity until realized. Realized gains and losses from the sale of available-for-sale securities, if any, are determined on a specific identification basis. A decline in the market value of any available-for-sale security below cost that is determined to be other than temporary results in a revaluation of its carrying amount to fair value. The impairment is charged to earnings and a new cost basis for the security is established. Premiums and discounts are amortized or accreted over the life of the related security as an adjustment to yield using the straight-line method. Interest income is recognized when earned.

Assets Measured at Fair Value on a Recurring Basis:

Accounting Standards Codification, or “ASC”, 820, *Fair Value Measurement* , or ASC 820, provides a single definition of fair value and a common framework for measuring fair value as well as disclosure requirements for fair value measurements used in financial statements. Under ASC 820, fair value is determined based upon the exit price that would be received by a company to sell an asset or paid by a company to transfer a liability in an orderly transaction between market participants, exclusive of any transaction costs. Fair value measurements are determined by either the principal market or the most advantageous market. The principal market is the market with the greatest level of activity and volume for the asset or liability. Absent a principal market to measure fair value, the Company uses the most advantageous market, which is the market from which the Company would receive the highest selling price for the asset or pay the lowest price to settle the liability, after considering transaction costs. However, when using the most advantageous market, transaction costs are only considered to determine which market is the most advantageous and these costs are then excluded when applying a fair value measurement. ASC 820 creates a three-level hierarchy to prioritize the inputs used in the valuation techniques to derive fair values. The basis for fair value measurements for each level within the hierarchy is described below, with Level 1 having the highest priority and Level 3 having the lowest.

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Quoted prices for similar assets or liabilities in active markets; quoted prices for identical or similar instruments in markets that are not active; and model-derived valuations in which all significant inputs are observable in active markets.

Level 3: Valuations derived from valuation techniques in which one or more significant inputs are unobservable.

Following are the major categories of assets measured at fair value on a recurring basis as of December 31, 2016 and 2015, using quoted prices in active markets for identical assets (Level 1), significant other observable inputs (Level 2), and significant unobservable inputs (Level 3) (in thousands):

December 31, 2016	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 188,543	$ —	$ —	$ 188,543
Marketable securities ─ corporate bonds	—	28,984	—	28,984
Marketable securities—commercial paper	—	5,998	—	5,998
	$ 188,543	$ 34,982	$ —	$ 223,525

December 31, 2015	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 29,166	$ —	$ —	$ 29,166
Marketable securities—corporate bonds	—	169,824	—	169,824
Marketable securities—commercial paper	—	2,996	—	2,996
Marketable securities—US government	—	11,500	—	11,500
	$ 29,166	$ 184,320	$ —	$ 213,486

The Company's investments in corporate bonds, commercial paper and U.S. government securities are exposed to price fluctuations. The fair value measurements for corporate bonds, commercial paper and U.S. government securities are based upon the quoted prices of similar items in active markets multiplied by the number of securities owned, exclusive of any transaction costs and without any adjustments to reflect discounts that may be applied to selling a large block of securities at one time.

Concentration of Risk:

Financial instruments, which potentially subject the Company to concentrations of credit risk, principally consist of cash and cash equivalents. The Company's cash and cash equivalents in excess of the Federal Deposit Insurance Corporation and the Securities Investor Protection Corporation insured limits at December 31, 2016, were approximately $199.0 million. The Company does not believe it is exposed to any significant credit risk due to the quality nature of the financial instruments in which the money is held. Pursuant to the Company's internal investment policy, investments must be rated A-1/P-1 or better by Standard and Poor's Rating Service and Moody's Investors Service at the time of purchase.

Property and Equipment:

Property and equipment are recorded at cost and depreciated over estimated useful lives ranging from three to five years using the straight-line method. Leasehold improvements are recorded at cost and amortized over the shorter of their useful lives or the term of the lease by use of the straight-line method. Maintenance and repair costs are charged to operations as incurred.

The Company assesses the impairment of long-lived assets, primarily property and equipment, whenever events or changes in business circumstances indicate that carrying amounts of the assets may not be fully recoverable. When such events occur, management determines whether there has been impairment by comparing the asset's carrying value with its fair value, as measured by the anticipated undiscounted net cash flows of the asset. Should impairment exist, the asset is written down to its estimated fair value. The Company recorded a loss from disposal of leasehold improvements during 2016 when it vacated one suite in its South San Francisco office location in favor of another suite. The Company has not recognized any impairment losses through December 31, 2016.

Research and Development Expenses:

Research and development expenses, or R&D, are charged to operations as incurred. The major components of research and development costs include clinical manufacturing costs, clinical trial expenses, consulting and other third-party costs, salaries and employee benefits, stock-based compensation expense, supplies and materials, and allocations of various overhead costs. Clinical trial expenses include, but are not limited to, investigator fees, site costs, comparator drug costs, and clinical research organization, or

CRO, costs. In the normal course of business, the Company contracts with third parties to perform various clinical trial activities in the ongoing development of potential products. The financial terms of these agreements are subject to negotiation and variations from contract to contract and may result in uneven payment flows. Payments under the contracts depend on factors such as the achievement of certain events, the successful enrollment of pa tients and the completion of portions of the clinical trial or similar conditions. The Company's accruals for clinical trials are based on estimates of the services received and efforts expended pursuant to contracts with numerous clinical trial sites, coo perative groups and CROs. The objective of the Company's accrual policy is to match the recording of expenses in the Consolidated Financial Statements to the actual services received and efforts expended. As actual costs become known, the Company adjusts i ts accruals in that period.

In instances where the Company enters into agreements with third parties for clinical trials and other consulting activities, upfront amounts are recorded to prepaid expenses and other in the accompanying Consolidated Balance Sheets and expensed as services are performed or as the underlying goods are delivered. If the Company does not expect the services to be rendered or goods to be delivered, any remaining capitalized amounts for non-refundable upfront payments are charged to expense immediately. Amounts due under such arrangements may be either fixed fee or fee for service, and may include upfront payments, monthly payments and payments upon the completion of milestones or receipt of deliverables.

Costs related to the acquisition of technology rights and patents for which development work is still in process are charged to operations as incurred and considered a component of research and development costs.

Research and Development Reimbursement:

The license agreement with the Licensor set a "cap" on the amount of external expenses the Company would incur, beginning January 1, 2012, in completing the clinical trials transferred from the Licensor to the Company. The license agreement originally stipulated that the Licensor would be responsible for all external expenses associated with the transferred clinical trials and that the Company would invoice for such costs on a quarterly basis. The Licensor had 60 days to review the invoice and supporting documentation. All amounts reimbursed from the licensor represent charges for services provided by third parties and not the Company. Accordingly, the Company has elected to treat the reimbursed costs as "pass-through" expenses billable to the Licensor and as an offset to R&D expenses. R&D expenses are recorded net of any excess cap costs billed to the Licensor. The Company recognized approximately $16.4 million of excess cap cost billed to the Licensor for the year ended December 31, 2013.

The license agreement was amended in July 2014 and made the Company solely responsible for the expenses incurred or accrued in conducting the ongoing legacy clinical trials after December 31, 2013. Pursuant to the amendment to the original license agreement, no reduction in the expenses related to the licensor legacy clinical trials that were in excess of the cap on such expenses set forth in the license agreement was recorded in the years ended December 31, 2016, 2015 and 2014.

Stock-Based Compensation:

Stock option awards:

ASC 718, *Compensation-Stock Compensation* , or ASC 718, requires the fair value of all share-based payments to employees, including grants of stock options, to be recognized in the statement of operations over the requisite service period. Under ASC 718, employee option grants are generally valued at the grant date and those valuations do not change once they have been established. The fair value of each option award is estimated on the grant date using the Black-Scholes Option Pricing Method. As allowed by ASC 718 for companies with a short period of publicly traded stock history, the Company's estimate of expected volatility is based on the average expected volatilities of a sampling of six companies with similar attributes to the Company, including industry, stage of life cycle, size and financial leverage. The risk-free rate for periods within the contractual life of the option is based on the U.S. Treasury yield curve in effect at the time of grant valuation. Option forfeitures are calculated when the option is granted to reduce the option expense to be recognized over the life of the award and updated upon receipt of further information as to the amount of options expected to be forfeited. The option expense is "trued-up" upon the actual forfeiture of a stock option grant. Due to its limited history, the Company uses the simplified method to determine the expected life of the option grants.

Performance shares:

The performance shares are valued on the grant date and the fair value of the performance award is equal to the market price of the Company's common stock on the grant date. The performance share expense is recognized based on the Company's estimate of a range of probabilities that the Company's closing common stock price will be lower or higher than the Company's common stock price on the grant date on the vesting dates. Based on the range of probabilities, the expense is calculated and recognized over the three-year vesting period.

Warrants:

Warrants granted to employees are normally valued at the fair value of the instrument on the grant date and are recognized in the statement of operations over the requisite service period. When the requisite service period precedes the grant date and a market condition exists in the warrant, the Company values the warrant using the Monte Carlo Simulation Method. When the terms of the warrant become fixed, the Company values the warrant using the Black-Scholes Option Pricing Method. As allowed by ASC 718 for companies with a short period of publicly traded stock history, the Company's estimate of expected volatility is based on the average volatilities of a sampling of eight to nine companies with similar attributes to the Company, including industry, stage of life cycle, size and financial leverage. The risk-free rate for periods within the contractual life of the warrant is based on the U.S. Treasury yield curve in effect at the time of grant valuation. In determining the value of the warrant until the terms are fixed, the Company factors in the probability of the market condition occurring and several possible scenarios. When the requisite service period precedes the grant date and is deemed to be complete, the Company records the fair value of the warrant at the time of issuance as an equity stock-based compensation transaction. The warrant is revalued each reporting period up to the grant date when the final fair value of the warrant is established and recorded. The grant date is determined when all pertinent information, such as exercise price and quantity are known.

Restricted stock units:

The restricted stock units, or RSUs, are valued on the grant date and the fair value of the RSUs is equal to the market price of the Company's common stock on the grant date. The RSU expense is recognized over the requisite service period. When the requisite service period begins prior to the grant date (because the service inception date occurs prior to the grant date), the Company is required to begin recognizing compensation cost before there is a measurement date (i.e., the grant date). The service inception date is the beginning of the requisite service period. If the service inception date precedes the grant date, accrual of compensation cost for periods before the grant date shall be based on the fair value of the award at the reporting date. In the period in which the grant date occurs, cumulative compensation cost shall be adjusted to reflect the cumulative effect of measuring compensation cost based on fair value at the grant date rather than the fair value previously used at the service inception date (or any subsequent reporting date).

Income Taxes:

The Company follows ASC 740, *Income Taxes* , or ASC 740 *,* which requires recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the consolidated financial statements or tax returns. Under this method, deferred tax assets and liabilities are based on the differences between the consolidated financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance to the extent management concludes it is more likely than not that the asset will not be realized. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled.

The standard addresses the determination of whether tax benefits claimed or expected to be claimed on a tax return should be recorded in the consolidated financial statements. Under ASC 740, the Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by the tax authorities, based on the technical merits of the position. The tax benefits recognized in the consolidated financial statements from such a position should be measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate settlement. ASC 740 also provides guidance on de-recognition, classification, interest and penalties on income taxes, accounting in interim periods and requires increased disclosures. At the date of adoption, and as of December 31, 2016 and 2015, the Company did not have a liability for unrecognized tax uncertainties.

The Company is subject to routine audits by taxing jurisdictions. As of December 31, 2016, the Company's tax years for 2013, 2014 and 2015 are subject to examination by the authorities. The Company's policy is to record interest and penalties on uncertain tax positions as income tax expense. As of December 31, 2016 and 2015, the Company had no accrued interest or penalties related to uncertain tax positions.

Net Loss per Common Share:

Basic net loss per common share is computed by dividing net loss applicable to common stockholders by the weighted average number of common shares outstanding during the periods presented as required by ASC 260, *Earnings per Share* . Diluted earnings per common share are the same as basic earnings per share because the assumed exercise of the Company's outstanding options are anti-dilutive. For the year ended December 31, 2016, potentially dilutive securities excluded from the calculations were 6,578,623 shares issuable upon exercise of options, 630,508 shares issuable upon the vesting of restricted stock units and 2,116,250 shares issuable upon exercise of a warrant. For the years ended December 31, 2015 and 2014, potentially dilutive securities excluded from the earnings per common share calculation were 7,668,007 and 6,113,318 shares, respectively, issuable upon exercise of options and warrants or issuable as performance awards.

Deferred Rent:

The Company has entered into operating lease agreements for its corporate offices in Los Angeles and South San Francisco that contain provisions for future rent increases, leasehold improvement allowances and rent abatements. The Company records monthly rent expense equal to the total of the payments due over the lease term, divided by the number of months of the lease term. The difference between the rent expense recorded and the amount paid is credited or charged to deferred rent, which is reflected as a separate line item in the accompanying Consolidated Balance Sheets. Additionally, the Company recorded as deferred rent the cost of the leasehold improvements paid by the landlord, which is amortized on a straight-line basis over the term of the lease.

Issuance of Common Stock Upon Exercise of Stock Option Grants:

When a stock option grant or partial stock option grant is exercised, the Company notifies its transfer agent to release the required number of common stock shares from the reserve for the Company's 2011 Incentive Award Plan. The Company records the transaction for the cash received and the issuance of common shares. Should there be a delay in the cash receipts due to the settlement period, the Company records a receivable from the exercise of an option as part of stockholders' equity on the Consolidated Balance Sheet.

Recently Issued Accounting Standards

In January 2016, the Financial Accounting Standards Board, or FASB, issued ASU No. 2016-01, *Recognition and Measurement of Financial Assets and Financial Liabilities* . The amendments in ASU 2016-01 address certain aspects of recognition, measurement, presentation and disclosure of financial instruments. ASU 2016-01 will be effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years. Early adoption of some of the amendments included in ASU 2016-01 for financial statements of fiscal years or interim periods that have not yet been issued is permitted as of the beginning of the fiscal year of adoption. The Company is currently evaluating the effect that the adoption of ASU 2016-01 will have on its consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* . The amendments in ASU 2016-02 will require organizations that lease assets, with lease terms of more than 12 months, to recognize on the balance sheet the assets and liabilities for the rights and obligations created by those leases. Consistent with current U.S. GAAP, the recognition, measurement, and presentation of expenses and cash flows arising from a lease by a lessee primarily will depend on its classification as a finance or operating lease. However, unlike current U.S. GAAP which requires only capital leases to be recognized on the balance sheet, ASU No. 2016-02 will require both types of leases to be recognized on the balance sheet. ASU 2016-02 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years. Early adoption is permitted. The Company is currently evaluating the effect that the adoption of ASU 2016-02 will have on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-06, *Derivatives and Hedging* (Topic 815): *Contingent Put and Call Options in Debt Instruments* . ASU 2016-06 amends FASB ASC 815-15 to clarify what steps are required when assessing whether the economic characteristics and risks of call (put) options are clearly and closely related to the economic characteristics and risks of their debt hosts, which is one of the criteria for bifurcating an embedded derivative. ASU 2016-06 will be effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years. An entity should apply the amendments in ASU No. 2016-06 on a modified retrospective basis to existing debt instruments as of the beginning of the fiscal year for which the amendments are effective. Early adoption is permitted, including adoption in an interim period. The Company is currently evaluating the effect that the adoption of ASU 2016-06 will have on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation – Stock Compensation* (Topic 718). ASU 2016-09 will require organizations to recognize all income tax effects of awards in the statement of operations when the awards vest or are settled. ASU 2016-09 will also allow organizations to repurchase more shares from employees than they could previously purchase for tax withholding purposes without triggering liability accounting and to make a policy election to account for forfeitures as they occur. ASU 2016-09 will be effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. Early adoption is permitted in any interim or annual period. The Company is currently evaluating the effect that the adoption of ASU 2016-09 will have on its consolidated financial statements.

In April 2016, the FASB issued ASU No. 2016-10, *Revenue from Contracts with Customers* (Topic 606). ASU 2016-10 amends ASC 606, *Revenue from Contracts with Customers* , to clarify two aspects of ASC 606, identifying performance obligations and the licensing implementation guidance, while retaining the related principles of those areas. The amendments in ASU 20 16-10 do not change the core principle of the guidance in ASC 606. The amendments in ASU No. 2016-10 affect the guidance in ASU 2014-09, Revenue from Contracts with Customers (Topic 606), which is not yet effective. The effective date and transition requir ements for the amendments in ASU No. 2016-10 are the same as the effective date and transition requirements in ASC 606 and any other Topic amended by ASU 2014-09. ASU 2015-14, *Revenue from Contracts with Customers* (Topic 606): *Deferral of the Effective Dat e* , defers the effective date of ASU 2014-09 by one year to annual reporting periods beginning after December 15, 2017, including interim reporting periods within that reporting period. The Company is currently evaluating the effect that the adoption of ASU 2016-10 will have on its consolidated financial statements.

In May 2016, the FASB issued ASU No. 2016-12, *Revenue from Contracts with Customers* (Topic 606). ASU 2016-12 amends ASC 606 to address certain issues in the guidance on assessing collectability, presentation of sales taxes, noncash consideration, and completed contracts and contract modifications at transition. The amendments in ASU 2016-12 do not change the core principle of the guidance in ASC 606. The amendments in ASU No. 2016-12 affect the guidance in ASU 2014-09, *Revenue from Contracts with Customers* (Topic 606), which is not yet effective. The effective date and transition requirements for the amendments in ASU No. 2016-12 are the same as the effective date and transition requirements in ASC 606 and any other Topic amended by ASU 2014-09. ASU 2015-14, *Revenue from Contracts with Customers* (Topic 606): *Deferral of the Effective Date* , defers the effective date of ASU 2014-09 by one year to annual reporting periods beginning after December 15, 2017, including interim reporting periods within that reporting period. The Company is currently evaluating the effect that the adoption of ASU 2016-12 will have on its consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows* (Topic 230) *: Classification of Certain Cash Receipts and Cash Payments* (a consensus of the Emerging Issues Task Force), which addresses the diversity in practice in how certain cash receipts and cash payments are presented and classified in the statement of cash flows. This update addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. ASU 2016-15 will be effective for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. The Company is currently evaluating the impact of adopting ASU 2016-15 on its consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows* (Topic 230): *Restricted Cash* that changes the presentation of restricted cash and cash equivalents on the statement of cash flows. Restricted cash and restricted cash equivalents will be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This amendment is effective for the Company in the fiscal year beginning December 15, 2017, but early adoption is permissible. The Company is currently evaluating the effect that the adoption of ASU 2016-18 will have on its consolidated financial statements.

Note 3—Prepaid Expenses and Other:

Prepaid expenses and other consisted of the following at December 31 (in thousands):

	2016	2015
Current:		
CRO services	$ 3,471	$ 2,969
Other clinical development	1,069	2,309
Insurance	1,159	1,138
Other	1,299	1,244
	6,998	7,660
Long-term:		
CRO services	5,077	5,754
Other clinical development	1,243	3,005
Insurance	40	87
Other	486	751
	6,846	9,597
Totals	$ 13,844	$ 17,257

Note 4—Property and Equipment:

Property and equipment consisted of the following at December 31 (in thousands):

Property and Equipment:	2016	2015
Leasehold improvements	$ 3,878	$ 1,502
Computer equipment	1,822	1,646
Telephone equipment	256	169
Furniture and fixtures	2,146	1,167
	8,102	4,484
Less: accumulated depreciation and amortization	(2,949)	(2,101)
Totals	$ 5,153	$ 2,383

Note 5—Accrued Expenses:

Accrued expenses consisted of the following at December 31 (in thousands):

	2016	2015
Accrued CRO/licensor services	$ 6,609	$ 8,436
Accrued other clinical development	7,015	3,618
Accrued legal fees	706	443
Accrued compensation	3,058	1,970
Other	38	172
Totals	$ 17,426	$ 14,639

Accrued CRO/licensor services and accrued other clinical development represent the Company's estimate of such costs as of December 31, 2016 and 2015, which will be adjusted in the period the actual costs become known.

Note 6—Stockholders' Equity:

Common Stock:

October 2012 Common Stock Offering. On October 18, 2012, the Company entered into an underwriting agreement with Merrill Lynch, Pierce, Fenner & Smith Incorporated and Leerink Swann, as representatives of several underwriters, providing for the offer and sale in a firm-commitment underwritten public offering of 7,500,000 shares of the Company's common stock, par value $0.0001 per share, at a price of $16.00 per share, less the underwriting discount. On October 19, 2012, the underwriters exercised the option granted to the underwriters to purchase an additional 1,125,000 shares of Company common stock from the Company at $16.00 per share, less the underwriting discount. The transactions were completed on October 24, 2012; the Company received net proceeds of approximately $129.2 million, which is comprised of gross proceeds of approximately $138 million, offset by the underwriting discount and estimated offering expenses of $8.8 million payable by the Company.

February 2014 Common Stock Offering. On February 10, 2014, the Company entered into an underwriting agreement with Merrill Lynch, Pierce, Fenner & Smith Incorporated, Citigroup, and Leerink Partners, as representatives of several underwriters, providing for the offer and sale in a firm-commitment underwritten public offering of 979,592 shares of the Company's common stock, par value $0.0001 per share, at a price of $122.50 per share, less the underwriting discount. On February 12, 2014, the underwriters exercised the option granted to the underwriters to purchase an additional 146,938 shares of Company common stock from the Company at $122.50 per share, less the underwriting discount. The transactions were completed on February 14, 2014; the Company received net proceeds of approximately $129.4 million, which is comprised of gross proceeds of approximately $138.0 million, offset by the underwriting discount and offering expenses of $8.6 million payable by the Company.

January 2015 Common Stock Offering. On January 21, 2015, the Company entered into an underwriting agreement with Merrill Lynch, Pierce, Fenner & Smith Incorporated and J.P. Morgan Securities, as representatives of several underwriters, providing for the offer and sale in a firm-commitment underwritten public offering of 1,000,000 shares of the Company's common stock, par value $0.0001 per share, at a price of $190.00 per share, less the underwriting discount. The underwriters exercised the option granted to the underwriters to purchase an additional 150,000 shares of Company common stock from the Company at $190.00 per share, less the underwriting discount. The transactions were completed on January 27, 2015; the Company received net proceeds of approximately $205.1 million, which is comprised of gross proceeds of approximately $218.5 million, offset by the underwriting discount and offering expenses of $13.4 million payable by the Company.

October 2016 Common Stock Offering. On October 19, 2016, the Company entered into an underwriting agreement in connection with the public offe ring, issuance and sale by the Company of 3,750,000 shares of the Company's common stock, par value $0.0001 per share, at a public offering price of $40.00 per share, less underwriting discounts and commissions. Under the terms of the underwriting agreeme nt, the Company also granted the underwriters an option exercisable for 30 days to purchase up to an additional 562,500 shares of its common stock at the public offering prices, less underwriting discounts and commissions. On October 20, 2016, the underwr iters exercised their option to purchase additional shares in full. The Company received net proceeds from the offering of approximately $161.9 million, after deducting underwriting discounts and commissions and estimated offering expenses.

The Company issued 46,668, 757,038, and 430,490 shares of common stock upon exercise of stock options during the years ended December 31, 2016, 2015 and 2014, respectively.

Authorized Shares:

The Company had 110,000,000 shares of stock authorized for issuance, of which 100,000,000 were common stock, par value $0.0001 per share, and 10,000,000 were preferred stock, par value $0.0001 per share. On October 4, 2011, the Board of Directors of the Company and the stockholders owning 100% of the Company's issued and outstanding common stock approved an Amended and Restated Certificate of Incorporation, or the Amended Certificate, which eliminated the Company's entire authorized class of preferred stock and reduced the total number of shares of capital stock that the Company may issue from 110,000,000 shares to 100,000,000 shares, all of which are designated as common stock, par value $0.0001 per share. The Amended Certificate became effective on November 14, 2011, upon the filing of the Amended Certificate with the Secretary of State of the State of Delaware.

Warrants:

Following the October 2011 common stock offering, Mr. Auerbach held approximately 21% of the 18,666,733 outstanding shares of the Company's common stock. Pursuant to the terms of the securities purchase agreement, the Company issued an anti-dilutive warrant to Mr. Auerbach, as the Company's founder. The warrant was issued to provide Mr. Auerbach with the right to maintain ownership of at least 20% of the Company's common stock in the event that the Company raised capital through the sale of its securities in the future.

In connection with the closing of a public offering on October 24, 2012, the exercise price and number of shares underlying the warrant issued to Mr. Auerbach were established and, accordingly, the final value of the warrant became fixed. Pursuant to the terms of the warrant, Mr. Auerbach may exercise the warrant to acquire 2,116,250 shares of the Company's common stock at $16 per share until October 4, 2021.

Performance Shares:

During January 2014, performance share awards were granted to certain employees that provide for a maximum of 28,411 common stock shares to be issued. These shares vest over three years on the first, second and third anniversary of December 15, 2013. On each vesting date, if the Company's closing common stock price is equal to $102.46 per share, one-third of the 28,411 shares will be awarded. If the Company's closing common stock price is either lesser or greater than $102.46 per share, the number of common stock shares to be issued will be adjusted to be less than one-third of the 28,411 shares. No shares will be awarded if the Company's closing common stock price is less than $47.53 per share at the vesting dates. The performance shares are valued on the grant date and the fair value of the performance award is equal to the market price of the Company's common stock on the grant date. The performance share expense is recognized based on the Company's estimate of a range of probabilities that the Company's closing common stock price will be lower or higher than $102.46 on the vesting dates. Based on the range of probabilities, the expense is calculated and recognized over the three-year vesting period. On December 15, 2016, the final vesting occurred and the calculations were performed. As a result, no shares of common stock were issued to the employees and the remaining 9,469 performance shares were cancelled. Previously, o n December 15, 2014 and December 15, 2015, the first and second vestings occurred and the calculations were performed. This resulted in 11,495 shares of common stock being issued to the employees and 7,447 performance shares being cancelled.

Stock Options:

The Company's 2011 Incentive Award Plan, or the 2011 Plan, was adopted by the Board of Directors on September 15, 2011. Pursuant to the 2011 Plan, the Company may grant incentive stock options and nonqualified stock options, as well as other forms of equity-based compensation. Incentive stock options may be granted only to employees, while consultants, employees, officers and directors are eligible for the grant of nonqualified options under the 2011 Plan. The maximum term of stock options granted under the 2011 Plan is 10 years. The exercise price of incentive stock options granted under the 2011 Plan must be at least equal to the fair value

of such shares on the date of grant. Through December 31, 2016, a total of 10,529,412 shares of the Company's common stock have been reserved for issuance under the 2011 Plan.

The Company awarded only "plain vanilla options" as determined by the SEC Staff Accounting Bulletin 107, or *Share Based Payment* . As of December 31, 2016, 7,209,131 shares of the Company's common stock are issuable upon the exercise of outstanding awards granted under the 2011 Plan and 1,741,857 shares of the Company's common stock are available for future issuance under the 2011 Plan. The fair value of options granted to employees was estimated using the Black-Scholes Option Pricing Method (see Note 2) with the following weighted-average assumptions used during the years ended December 31:

	2016	2015	2014
Dividend yield	0.0%	0.0%	0.0%
Expected volatility	68.1%	64.5%	74.4%
Risk-free interest rate	1.7%	1.6%	1.8%
Expected life in years	5.80	5.82	5.85

Employee stock-based compensation was as follows for the years ended December 31 (in thousands except per share data):

	2016	2015	2014
Stock-based compensation:			
Options-			
Research and development, or R&D	$ 88,049	$ 76,995	$ 28,446
General and administrative, or G&A	25,043	17,166	9,154
Restricted stock units-			
G&A	1,580	—	—
R&D	3,120	—	—
Performance shares: R&D	(528)	773	1,551
Total share-based compensation expense	$ 117,264	$ 94,934	$ 39,151
Impact on basic and diluted net loss per share	$ 3.52	$ 2.96	$ 1.30
Weighted average shares (basic and diluted)	33,295,114	32,126,094	30,010,979

Activity with respect to options granted under the 2011 Plan is summarized as follows:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2013	2,604,224	$ 23.31	8.9	$ 208,902
Granted	1,980,208	$ 159.62	9.2	—
Forfeited	(175,816)	$ 67.08	—	—
Exercised	(430,490)	$ 17.12	—	$ 74,109
Outstanding at December 31, 2014	3,978,126	$ 89.55	8.7	$ 431,635
Granted	2,606,183	$ 117.62	9.4	—
Forfeited	(277,140)	$ 177.98	—	—
Exercised	(757,038)	$ 36.19	—	$ 102,149
Expired	(7,846)	$ 105.42		
Outstanding at December 31, 2015	5,542,285	$ 105.59	8.6	$ 87,632
Granted	1,658,465	$ 42.34	9.3	
Forfeited	(446,544)	$ 122.50		
Exercised	(43,751)	$ 13.16		$ 1,360
Expired	(131,933)	$ 185.10		
Outstanding at December 31, 2016	6,578,522	$ 87.52	8.0	$ 18,442
Unvested at December 31, 2016	3,106,083	$ 80.00	9.1	$ 171
Exercisable at December 31, 2016	3,472,439	$ 94.24	7.0	$ 18,271

At December 31, 2016, total estimated unrecognized employee compensation cost related to non-vested stock options granted prior to that date was approximately $132.1 million, which is expected to be recognized over a weighted-average period of 1.7 years.

At December 31, 2016 , the total estimated unrecognized employee compensation cost related to non-vested restricted stock units was approximately $29.7 million, which is expected to be recogn ized over a weighted-average period of 2.6 years. The weighted-average grant date fair value of options granted during the years ended December 31, 2016, 2015 and 2014, was $25.69, $68.30 and $101.17 per share, respectively. The weighted average grant da te fair value of restricted stock units awarded during the year ended December 31, 2016, was $54.35.

Stock options	Shares	Weighted Average Grant-Date Fair Value
Nonvested shares at December 31, 2015	3,572,202	$ 73.59
Granted	1,658,465	25.69
Vested/Issued	(1,678,040)	77.69
Forfeited	(446,544)	73.22
Nonvested shares at December 31, 2016	3,106,083	$ 47.78

Performance shares	Shares	Weighted Average Grant-Date Fair Value
Nonvested shares at December 31, 2015	9,469	$ 102.46
Granted	—	102.46
Vested/Issued	—	102.46
Cancelled	(9,469)	102.46
Nonvested shares at December 31, 2016	—	$ 102.46

Restricted stock units	Shares	Weighted Average Grant-Date Fair Value
Nonvested shares at December 31, 2015	—	$ —
Granted	640,644	54.35
Vested/Issued	(2,917)	54.35
Cancelled	(7,219)	54.35
Nonvested shares at December 31, 2016	630,508	$ 54.35

Note 7—401(k) Savings Plan:

During 2012, the Company adopted a 401(k) savings plan for the benefit of its employees. The Company is required to make matching contributions to the 401(k) plan equal to 100% of the first 3% of wages deferred by each participating employee and 50% on the next 2% of wages deferred by each participating employee. The Company incurred expenses for employer matching contributions of approximately $1.0 million, $0.7 million and $0.5 million for the years ended December 31, 2016, 2015 and 2014, respectively.

N ote 8—Income Taxes:

Temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes give rise to the Company's deferred income taxes. The components of the Company's net deferred tax assets as of December 31, 2016 and 2015 are as follows (in thousands):

	Federal	State	Total
Deferred tax assets—2016:			
Net operating loss carry forwards	$ 178,654	$ 30,654	$ 209,308
Business credit carryforwards	14,257	6,999	21,256
Organization costs	151	26	177
Compensation	71,987	12,354	84,341
Deferred rent - leasehold improvement	1,019	175	1,194
Other	852	145	997
	266,920	50,353	317,273
Deferred tax liabilities	(1,083)	(186)	(1,269)
Total deferred tax assets	265,837	50,167	316,004
Valuation allowance	(265,837)	(50,167)	(316,004)
Net deferred tax assets	$ —	$ —	$ —

	Federal	State	Total
Deferred tax assets—2015:			
Net operating loss carry forwards	$ 125,244	$ 21,489	$ 146,733
Business credit carryforwards	11,528	6,373	17,901
Organization costs	166	29	195
Compensation	38,138	6,545	44,683
Depreciation	180	30	210
Other	53	9	62
	175,309	34,475	209,784
Deferred tax liabilities	—	—	—
Total deferred tax assets	175,309	34,475	209,784
Valuation allowance	(175,309)	(34,475)	(209,784)
Net deferred tax assets	$ —	$ —	$ —

As the ultimate realization of the potential benefits of the Company's deferred tax assets is considered unlikely by management, the Company has offset the deferred tax assets attributable to those potential benefits through valuation allowances. Accordingly, the Company did not recognize any benefit from income taxes in the accompanying Consolidated Statements of Operations to offset its pre-tax losses. The valuation allowance increased $106.2 million in 2016 and $101.4 million in 2015. At December 31, 2016, the Company had federal and state net operating loss carryforwards of approximately $525.5 million each, which will begin to expire in 2031. At December 31, 2016, the Company also has federal and state research and development credit carryforwards of approximately $14.3 million and $10.6 million, respectively. Pursuant to the Internal Revenue Code, Sections 382 and 383, use of the Company's net operating loss and credit carryforwards could be limited if a cumulative change in ownership of more than 50% occurs within a three-year period. The Company has not yet performed an assessment on the potential limitation on net operating loss and credit carryforwards.

As a result of certain realization requirements of ASC 718, the table of deferred tax assets and liabilities shown above does not include certain deferred tax assets as of December 31, 2016 and 2015 that arose directly from (or the use of which was postponed by) tax deductions related to equity compensation in excess of compensation recognized for financial reporting. Those deferred tax assets include federal and state net operating losses. Equity will be increased by approximately $0.1 million if and when such deferred tax assets are ultimately realized. The Company uses ASC 740 ordering when determining when excess tax benefits have been realized.

The provision (credit) for income taxes in the accompanying Consolidated Statements of Operations differs from the amount calculated by applying the statutory income tax rate t o income (loss) from continuing operations before income taxes. The primary components of such differences are as follows as of December 31 (in thousands):

	2016	2015	2014
Tax computed at the federal statutory rate	$ (93,839)	$ (81,356)	$ (48,268)
State taxes	(15,693)	(16,620)	(8,465)
Permanent items	6,152	4,225	9,956
R&D credits	(2,728)	(5,029)	(3,697)
Other	(113)	(2,571)	690
Change in valuation allowance	106,221	101,351	49,784
Total provision	$ —	$ —	$ —

The following is a tabular reconciliation of the total amounts of unrecognized tax benefits at December 31:

(in thousands)	2016	2015	2014
Unrecognized tax benefits—January 1	$ 4,475	$ 2,482	$ 1,263
Gross decreases—tax positions in prior period	—	—	(205)
Gross increases—tax positions in current period	840	1,993	1,424
Unrecognized tax benefits—December 31	$ 5,315	$ 4,475	$ 2,482

The unrecognized tax benefits that, if recognized, would affect the effective tax rate is zero at December 31, 2015. The Company does not have tax positions for which it is reasonably possible that the total amounts of unrecognized tax benefit will significantly increase or decrease within 12 months of the reporting date.

Note 9—Commitments and Contingencies:

Office Leases:

On December 7, 2011, the Company, entered into a non-cancelable operating lease for office space. The initial term of the lease is for seven years and commenced on December 10, 2011. The base rent was approximately $44,400 per month during the first year and will increase each year during the initial term, up to approximately $53,000 per month during the seventh year. The lease has an expiration date of December 9, 2018. In addition, the Company has an option to extend the lease for an additional five-year term. The lease is subject to additional charges for common area maintenance and other costs. Concurrent with the execution of the lease, the Company provided the landlord an automatically renewable stand-by letter of credit in the amount of $2,500,000. The stand-by letter of credit is collateralized by a high-yield savings account which is classified as restricted cash on the accompanying Consolidated Balance Sheets. Rent expense for the years ended December 31, 2016, 2015, and 2014, was approximately $3,547,300, $1,597,200 and $1,126,700, respectively.

On June 7, 2012, the Company entered into a long-term lease agreement for office space in South San Francisco, California. The initial term of the lease is seven years and commenced on November 1, 2012. The base rent was approximately $20,250 per month during the first year and will increase over the course of the initial term, up to approximately $30,820 per month during the seventh year. In addition, the Company has an option to extend the lease for an additional five-year term, which would commence upon the expiration of the initial term. In the event the Company elects to extend the lease, the minimum monthly rent payable for the additional term will be the then-current fair market rent calculated in accordance with the terms of the lease. The Company provided the landlord an automatically renewable stand-by letter of credit in the amount of $1,591,400. The stand-by letter of credit is collateralized by a high-yield savings account which is classified as restricted cash on the accompanying Consolidated Balance Sheets.

On November 28, 2012, the Company entered into an amendment to the lease for its office space in Los Angeles, California. This amendment added approximately 3,500 rentable square feet to the existing lease of approximately 13,250 square feet. Pursuant to the amendment, the Company’s monthly rent increased by approximately $12,145 per month following the execution of the amendment and will be increased to approximately $14,080 per month at the end of the lease term.

On December 1, 2013, the Company entered into a second amendment to the lease for its office space in Los Angeles, California. This amendment added approximately 5,949 rentable square feet to the existing lease of approximately 16,750 square feet. Pursuant to the amendment, the Company’s monthly rent increased by approximately $10,400 per month following the execution of the amendment and will be increased to approximately $25,100 per month at the end of the lease term.

On March 18, 2014, the Company entered into a third amendment to the lease of its office space in Los Angeles, California. This amendment added approximately 2,908 rentable square feet to the existing lease of approximately 22,775 square feet. Pursuant to the amendment, the Company's monthly rent expense increased b y approximately $11,487 per month following the execution of the amendment and will be increased to approximately $12,928 per month at the end of the lease term.

On May 19, 2014, the Company entered into a first amendment to the lease of its office space in South San Francisco, California. This amendment added approximately 7,152 rentable square feet to the existing lease of approximately 9,560 square feet. Pursuant to the amendment, the Company's monthly rent expense increased by approximately $22,886 per month following the execution of the amendment and will be increased to approximately $27,328 per month during the last year of the lease term.

In July 2015, the Company amended its lease with CA-10880 Wilshire Limited Partnership to expand the rented square feet in its Los Angeles office by approximately 26,000 square feet. The lease commenced April 1, 2016, and increased the monthly rent in the Los Angeles location by approximately $150,000 per month with annual increases of approximately 3% per year for the 10-year lease term. The amendment also extended the term of the lease until March 2026.

In addition, in July 2015, the Company amended its office lease with PR 701 Gateway, LLC (as successor in interest to DWF III Gateway, LLC) to expand the rented square feet in its South San Francisco location by approximately 13,000 square feet. The lease commenced April 1, 2016, and increased the monthly rent in the South San Francisco location by approximately $51,400 with annual increases of approximately 3% per year for the 10-year lease term. The amendment also extended the term of the lease until March 2026.

Future minimum lease payments for each of the years subsequent to December 31, 2016, are as follows (in thousands):

Year Ending December 31,	Amount
2017	$ 3,977
2018	4,096
2019	4,219
2020	4,345
Thereafter	24,733
Total	$ 41,370

License Agreement:

In August 2011, the Company entered into an agreement pursuant to which Pfizer, Inc., or the Licensor, agreed to grant it a worldwide license for the development, manufacture and commercialization of PB272 neratinib (oral), PB272 neratinib (intravenous) and PB357, and certain related compounds. The license is exclusive with respect to certain patent rights owned by or licensed to the Licensor. Under the agreement, the Company is obligated to commence a new clinical trial for a product containing one of these compounds within a specified period of time and to use commercially reasonable efforts to complete clinical trials and to achieve certain milestones as provided in a development plan. From the closing date of the agreement through December 31, 2011, the Licensor continued to conduct the existing clinical trials on behalf of the Company at the Licensor's sole expense. At the Company's request, the Licensor has agreed to continue to perform certain services in support of the existing clinical trials at the Company's expense. These services will continue through the completion of the transitioned clinical trials. The license agreement "capped" the out of pocket expense the Company would be responsible for completing the then existing clinical trials. All agreed upon costs incurred by the Company above the "cost cap" would be reimbursed by the Licensor. The Company exceeded the "cost cap" during the fourth quarter of 2012. In accordance with the license agreement, the Company billed the Licensor for agreed upon costs above the "cost cap" until December 31, 2013.

On July 18, 2014, the Company entered into an amendment to the license agreement with the Licensor. The amendment amends the License Agreement to (1) reduce the royalty rate payable by the Company to the Licensor on sales of licensed products; (2) release the Licensor from its obligation to pay for certain out-of-pocket costs incurred or accrued on or after January 1, 2014 to complete certain ongoing clinical studies; and (3) provide that the Licensor and the Company will continue to cooperate to effect the transfer to the Company of certain records, regulatory filings, materials and inventory controlled by Licensor as promptly as reasonably practicable.

As consideration for the license, the Company is required to make substantial payments upon the achievement of certain milestones totaling approximately $187.5 million if all such milestones are achieved. Should the Company commercialize any of the compounds licensed from the Licensor or any products containing any of these compounds, the Company will be obligated to pay to the Licensor annual royalties at a fixed rate in the low-to-mid teens of net sales of all such products, subject to certain reductions and offsets in some circumstances. The Company's royalty obligation continues, on a product-by-product and country-by-country basis,

until the later of (1) the last to expire licensed patent covering the applicable licensed product in such country, or (2) the earlier of generic competition for such licensed product reaching a certain level in such country or expiration of a certain time period after first c ommercial sale of such licensed product in such country. In the event that the Company sublicenses the rights granted to the Company under the license agreement with the Licensor to a third party, the same milestone and royalty payments are required. The C ompany can terminate the license agreement at will at any time after April 4, 2013, or for safety concerns, in each case upon specified advance notice.

Clinical Trial Contracts:

The Company engages with clinical research organizations and contract manufacturing organizations, or CMOs, in addition to engaging in contracts for the management of its ongoing clinical trials and pre-commercialization efforts. The Company may cancel these agreements with a 30 to 45 day written notice to the outside vendor. The Company would be obligated to pay for services rendered up to that point. The contracts also contain variable costs that are hard to predict as they are based on such things as patients enrolled and clinical trial sites, which can vary and therefore, are not included in the table below. The contracts held by the Company as of December 31, 2016, are summarized as follows (in thousands):

Indication	Estimated Contractual Obligations as of December 31, 2016	Months Remaining on Contract
HER2 Overexpressed/Amplified Breast Cancer (Extension)	$ 22,844	20
HER2 Overexpressed/Amplified Breast Cancer (Licensor Legacy Clinical Trials)	1,541	12
HER2 Mutated Non-Small Cell Lung Cancer	338	12
HER2 Mutated Breast Cancer and HER2 Mutated Breast Cancer with Brain Mets	3,962	18
Metastatic & Adjuvant Breast Cancer	47,865	21
Neoadjuvant Breast Cancer	4,537	20
Preclinical Research	22,557	13
HER2 Mutated Solid Tumors	12,946	12
Other	6,487	12
Total	$ 123,077	

Included in the above are payments to be made when milestones are reached. As of December 31, 2016, Company obligations for potential milestone payments totaled approximately $22.7 million. This amount will be paid by the Company if all milestones are reached and would reduce the overall contractual obligation if one or more milestone is never reached.

Legal Proceedings :

The Company currently has four pending legal proceedings in which it is named as a defendant. On June 3, 2015, Hsingching Hsu, individually and on behalf of all others similarly situated, filed a class action lawsuit against the Company and certain of its executive officers in the United States District Court for the Central District of California (Case No. 8:15-cv-00865-AG-JCG). On October 16, 2015, lead Plaintiff Norfolk Pension Fund filed an amended complaint on behalf of all persons who purchased the Company’s securities between July 22, 2014 and May 29, 2015. The amended complaint alleges that the Company and certain of its executive officers made false and/or misleading statements and failed to disclose material adverse facts about the Company’s business, operations, prospects and performance in violation of Sections 10(b) (and Rule 10b-5 promulgated thereunder) and 20(a) of the Exchange Act. The plaintiff seeks damages, interest, costs, attorneys' fees, and other unspecified equitable relief. On November 30, 2015, the Company filed a motion to dismiss the amended complaint. The plaintiff opposed this motion, and the court heard oral argument on March 14, 2016. On September 30, 2016, the court denied the Company’s motion to dismiss. The court set a trial for November 6, 2018.

O n February 2, 2016, Fredric N. Eshelman filed a lawsuit against the Company's Chief Executive Officer and President, Alan H. Auerbach, and the Company in the United States District Court for the Eastern District of North Carolina (Case No. 7:16-cv-00018-D) . The complaint generally alleges that Mr. Auerbach and the Company made defamatory statements regarding Dr. Eshelman in connection with a proxy contest. Dr. Eshelman seeks compensatory and punitive damages and expenses and costs, including attorneys' fe es. On April 4, 2016, the defendants filed a motion to dismiss the complaint. On May 2, 2016, Dr. Eshelman filed a notice of voluntary dismissal of the claims against Mr. Auerbach. On February 6, 2017, the court denied the Company's motion to dismiss. On February 21, 2017, the Company filed an answer to Dr. Eshelman's complaint and brought counterclaims against Dr. Eshelman for defamatory statements regarding the Company made by him in connection with the proxy contest. The court has set a schedule for discovery to be conducted through September 2017.

On April 12 and April 14, 2016, alleged shareholders filed two derivative lawsuits purportedly on behalf of the Company against certain of the Company's officers and directors in the Superior Court of the State of California, Los Angeles, captioned Xing Xie v. Alan H. Auerbach, et al., No. BC616617, and Kevin McKenney v. Auerbach, et al., No. BC617059. The complaints assert claims for breach of fiduciary duty, unjust enrichment, abuse of control, mismanagement and waste of corporate assets arising from substantially similar allegations as those contained in the putative securities class action described above. The complaints seek an unspecified sum of damages and equitable relief.

The Company believes that these cases are without merit and the Company intends to vigorously defend itself against these cases. It is impossible to determine a potential dollar figure for the lawsuits as a contingent loss.

Note 10—Quarterly Financial Data:

Quarterly financial data (in thousands except share and per share data):

(unaudited)	**Three Months Ended**			
	March 31,	**June 30,**	**September 30,**	**December 31,**
2016				
Revenues	$ —	$ —	$ —	$ —
Net loss	(70,972)	(66,597)	(65,781)	(72,661)
Net loss applicable to common stock	(70,972)	(66,597)	(65,781)	(72,661)
Net loss per share—basic and diluted	$ (2.19)	$ (2.05)	$ (2.02)	$ (2.04)
Weighted-average common shares outstanding—basic and diluted	32,478,408	32,493,092	32,497,168	35,694,193
2015				
Revenues	$ —	$ —	$ —	$ —
Net loss	(52,454)	(64,694)	(60,417)	(61,719)
Net loss applicable to common stock	(52,454)	(64,694)	(60,417)	(61,719)
Net loss per share—basic and diluted	$ (1.66)	$ (2.01)	$ (1.87)	$ (1.90)
Weighted-average common shares outstanding—basic and diluted	31,588,315	32,158,108	32,303,203	32,444,270
2014				
Revenues	$ —	$ —	$ —	$ —
Net loss	(19,794)	(38,844)	(35,844)	(47,483)
Net loss applicable to common stock	(19,794)	(38,844)	(35,844)	(47,483)
Net loss per share—basic and diluted	$ (0.67)	$ (1.29)	$ (1.19)	$ (1.57)
Weighted-average common shares outstanding—basic and diluted	29,567,071	30,117,819	30,117,819	30,232,718

Exhibit 21.1

Puma Biotechnology, Inc.
Subsidiaries

Subsidiary	Jurisdiction of Incorporation or Organization
Puma Biotechnology Ltd	England and Wales

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-3 (No. 333-201603), in the Post-Effective Amendment No. 2 to Form S-1 on Form S-3 (No. 333-178308), and in the Registration Statements on Form S-8 (Nos. 333-181703, 333-196993 and 333-205117), pertaining to the Puma Biotechnology, Inc. 2011 Incentive Award Plan, as amended, of our report dated March 1, 2017, relating to the consolidated financial statements of Puma Biotechnology, Inc. and Subsidiary and the effectiveness of internal control over financial reporting of Puma Biotechnology, Inc. and Subsidiary included in the Annual Report on Form 10-K for the year ended December 31, 2016.

San Diego, California
March 1, 2017

/s/ PKF
PKF
Certified Public Accountants
A Professional Corporation

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Alan H. Auerbach, certify that:

1. I have reviewed this Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2017

/s/ Alan H. Auerbach
Alan H. Auerbach
Principal Executive Officer

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Charles R. Eyler, certify that:

1. I have reviewed this Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2017

/s/ Charles R. Eyler
Charles R. Eyler
Principal Financial and Accounting Officer

Exhibit 32.1

CERTIFICATION
PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

The following certification is being furnished solely to accompany the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016, pursuant to 18 U.S.C. § 1350 and in accordance with SEC Release No. 33-8238. This certification shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be incorporated by reference in any filing of Puma Biotechnology, Inc. under the Securities Act of 1933, as amended, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Certification of Principal Executive Officer

I, Alan H. Auerbach, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016, fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended, and that the information contained in such report fairly presents, in all material respects, the financial condition and results of operations of Puma Biotechnology, Inc.

Date: March 1, 2017

/s/ Alan H. Auerbach
Alan H. Auerbach
Principal Executive Officer

A signed original of this written statement required by Section 906 has been provided to Puma Biotechnology, Inc. and will be retained by Puma Biotechnology, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

Exhibit 32.2

CERTIFICATION
PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

The following certification is being furnished solely to accompany the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016, pursuant to 18 U.S.C. § 1350 and in accordance with SEC Release No. 33-8238. This certification shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be incorporated by reference in any filing of Puma Biotechnology, Inc. under the Securities Act of 1933, as amended, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Certification of Principal Financial Officer

I, Charles R. Eyler, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2016, fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended, and that the information contained in such report fairly presents, in all material respects, the financial condition and results of operations of Puma Biotechnology, Inc.

Date: March 1, 2017

/s/ Charles R. Eyler
Charles R. Eyler
Principal Financial and Accounting Officer

A signed original of this written statement required by Section 906 has been provided to Puma Biotechnology, Inc. and will be retained by Puma Biotechnology, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.