PUMA BIOTECHNOLOGY, INC.
Form 10-K
March 09, 2018

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, 2017

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, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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 $2,481,469,190 as of June 30, 2017, based upon the closing price of $87.40 per share of the registrant's common stock on the NASDAQ Global Select Market on Friday, June 30, 2017, 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 20, 2018, there were 37,719,724 shares of the registrant's common stock outstanding.

Documents Incorporated by Reference:

Portions of the Proxy Statement for the registrant's 2018 Annual Meeting of Stockholders, or the 2018 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 commercialization of NERLYNX® (neratinib);
- 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;
- our use of clinical research organizations and other contractors;
- our ability to find collaborative partners for research, development and commercialization of potential products;
- efforts of our licensees to obtain regulatory approval and commercialize NERYLNX in areas outside the United States;
- 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 state 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” in Part I 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 the section entitled “Item 1A. Risk Factors” in Part I of this Annual Report, 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.

PART I

ITEM 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 U.S. commercialization of NERLYNX (neratinib), our first U.S. Food and Drug Administration, or FDA, approved product, and on the further development of the oral version of neratinib for additional indications in 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. Until recently, we have focused our efforts and resources primarily on obtaining regulatory approval for NERLYNX (neratinib) and on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel.

On July 17, 2017, we received regulatory approval of our first product, NERLYNX (neratinib), formally known as PB 2727 (neratinib (oral)), for the extended adjuvant treatment of adult patients with early state HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy from the FDA. After receiving FDA approval, we commenced commercialization of NERLYNX in the United States using a direct sales force.

Before we can market neratinib in countries outside the United States, we must receive regulatory approval from the appropriate government entities in those countries. We filed a Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, in July 2016. We recently announced that the EMA's Committee for Medicinal Products for Human Use, or CHMP, adopted a negative opinion and recommend refusal of our MAA for neratinib for the extended adjuvant treatment of early stage HER2-positive breast cancer. We have 15 days from the date of acknowledgement of receipt of the final opinion package to request a re-examination, and we intend to submit the request within the prescribed timeline. We recently entered into exclusive license agreements with Specialised Therapeutics Asia Pte Ltd., or STA, Medison Pharma Ltd., or Medison, and CANbridgepharma Limited, or CANbridge, to pursue regulatory approval and commercialize NERLYNX, if approved, in South East Asia, Israel and greater China, respectively. We plan to continue to pursue commercialization of NERLYNX in other countries outside the United States, if approved, and will evaluate various commercialization options in those countries, including developing a direct sales force, contracting with third parties to provide sales and marketing capabilities, or some combination of these two options. We expect that our expenses will continue to increase as we continue commercialization efforts.

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 type of breast cancer by binding to the HER2

protein. There are 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.

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 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. We expect to report the top line data from this trial in 2018.

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 enables 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. In order for patients to qualify for our managed access program they must be unable to participate in any ongoing neratinib clinical trial. 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 EGFR exon 18, HER2 of HER4 mutation;
- 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.

We license the commercial rights to our current drug candidates from Pfizer, Inc., Pfizer or the Licensor, 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 primary objective is to build neratinib into a significant oncology franchise as a single agent, and potentially in combination with other therapies. The following elements comprise the strategy to achieve this objective:

- Seek regulatory approval and commence commercialization of neratinib in regions outside the United States. Before we can market neratinib outside the United States for any indication, including the FDA-approved indication associated with NERLYNX, we must obtain regulatory approval in those countries. We recently entered into exclusive license agreements with STA, Medison, and CANbridge pursuant to which each will develop and commercialize NERLYNX in South East Asia, Israel, and greater China, respectively. Pursuant to these agreements we receive upfront and milestone payments and will receive royalties on sales once commercialized. In June 2016, we submitted an MAA to the EMA 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 submission was 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. The CHMP recently recommended refusal of our MAA for neratinib for the extended adjuvant treatment of early stage HER2-positive breast cancer but allowed us to request a re-examination, which we intend to do. We are continuing to also evaluate potential commercialization options for the extended adjuvant setting in additional countries outside the United States, 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.

- Continue to advance the development of neratinib for the treatment of other HER2-positive or HER2 mutated breast cancer indications. We are primarily focused on developing neratinib for the treatment of patients with HER2-positive breast cancer, HER2-negative breast cancer with a HER2 mutation or other solid tumors with an activating mutation in HER2, or patients with 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 approaches 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. We are currently commercializing NERLYNX using a direct sales force in the United States and using out-licenses in certain countries outside of the United States. As we move additional 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 type of breast 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, the combination of pertuzumab plus trastuzumab and chemotherapy was

recently approved as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence based on the results of the APHINITY trial. We are also aware of the KAITLIN trial, which is comparing trastuzumab plus pertuzumab plus taxane following anthracyclines versus T-DM1 plus pertuzumab following anthracyclines as an adjuvant therapy.

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 the 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. The number of patients with third line or later HER2 positive metastatic breast cancer may decrease in future years as the introduction of new neoadjuvant, adjuvant and extended adjuvant treatments may reduce the number of patients with recurrence of HER2 positive breast cancer and therefore reduce the number of patients with HER2 positive metastatic breast cancer. In 2013, worldwide sales of Tykerb for this indication were approximately $325 million.

We believe that approximately 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 (approximately 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 September 2017, we presented updated data from the ExteNET trial at the European Society of Medical Oncology (ESMO) 2017 Congress in Madrid, Spain. The data represented a predefined 5-year invasive disease free survival (iDFS) analysis as a follow-up to the primary 2-year iDFS analysis of the Phase III ExteNet trial. The results of the trial demonstrated that after a median follow up of 5.2 years, treatment with neratinib resulted in a 27% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.73, p = 0.008). The 5-year iDFS rate for the neratinib arm was 90.2% and the 5-year iDFS rate for the placebo arm was 87.7%. The secondary endpoint of the trial was invasive disease free survival including ductal carcinoma in situ (iDFS-DCIS). The results of the trial demonstrated that treatment with neratinib resulted in a 29% reduction of risk of disease recurrence, including DCIS or death versus placebo (hazard ratio = 0.71, p = 0.004). The 5-year iDFS-DCIS rate for the neratinib arm was 89.7% and the 5-year iDFS-DCIS rate for the placebo arm was 86.8%.

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 40% reduction of risk of invasive disease recurrence or death versus placebo (hazard ratio = 0.60, p = 0.002). The 5-year iDFS rate for the neratinib arm was 91.2% and the 5-year iDFS rate for the placebo arm was 86.8%. For the pre-defined subgroup of patients with hormone receptor negative disease, the results of the trial demonstrated that treatment with neratinib resulted in a hazard ratio of 0.95 (p = 0.762).

The safety results were unchanged from the primary 2-year iDFS analysis of the study that showed 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.

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 was pCR in the breast and the lymph nodes at the time of surgery. The goal of the trial was to match investigational regimens with patient subsets on the basis of molecular characteristics, referred to as biomarker signatures, that benefit 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.

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 Antonio 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 . 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 neratinib 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 patients in 33 countries with locally recurrent or metastatic breast cancer who had not received prior anticancer therapy for locally recurrent or metastatic disease. Patients were randomized to receive first-line treatment with either paclitaxel plus neratinib or paclitaxel plus trastuzumab. The primary endpoint of the trial was progression free survival. The secondary endpoints of the study included objective response rate and the incidence of central nervous system (CNS) metastases, including brain metastases.

The results of the trial demonstrated that the 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 an 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. We expect to report the top line data from this trial in 2018.

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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 prior 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, determined 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 cohort 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 at 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 loperamide 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 diarrhea. 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 included in the safety population. For the patients in the DE cohort, thus far 47% of the patients have been able to dose escalate temsirolimus from 8 mg per week to 15 mg per week. 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 the DE cohort, the efficacy results from the trial demonstrated that 11 patients (30%) experienced a PR.

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 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 PR, 4 (10%) patients experienced prolonged stable disease (SD) for greater than or equal to 6 months and 12 (30%) patients experienced 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.

In June 2017, we presented additional data from this trial at the ASCO 2017 Annual Meeting. The multicenter Phase II clinical trial enrolled patients with HER2-positive metastatic breast cancer who have brain metasteses. The trial enrolled three cohorts of patients. Patients in the second cohort (n=5) represent patients who had brain metastases which were amenable to surgery and who were administered neratinib monotherapy prior to and after surgical

resection. The third cohort (target enrollment=60) enrolled two sub-groups of patients (prior lapatinib-treated and no prior lapatinib) with progressive brain metastases who were administered neratinib in combination with the chemotherapy drug capecitabine. The oral presentation reflected only the patients in the third cohort of patients without prior lapatinib exposure (cohort 3A, n=37), who all had progressive brain metastases at the time of enrollment and who received the combination of capecitabine plus neratinib. Results from the second cohort and cohort 3B (prior lapatinib-treated) will be presented at a forthcoming medical meeting.

In cohort 3A, 30% of the patients had received prior craniotomy, 65% of the patients had received prior whole brain radiotherapy (WBRT), and 35% had received prior stereotactic radiosurgery (SRS) to the brain. No patients had received prior treatment with lapatinib.

The primary endpoint of the trial was central nervous system (CNS) Objective Response Rate according to a composite criteria that included volumetric brain MRI measurements, steroid use, neurological signs and symptoms, and RECIST evaluation for non-CNS sites. The secondary endpoint of the trial was CNS response by Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria. The efficacy results from the trial showed that 49% of patients experienced a CNS Objective Response by the composite criteria. The results also showed that the CNS response rate using the RANO-BM criteria was 24%. The median time to CNS progression was 5.5 months and the median overall survival was 13.5 months, though 49% of patients remain alive and survival data are immature.

The results for cohort 3A showed that the most frequently observed severe adverse event for the 37 patients evaluable for safety was diarrhea. Patients received antidiarrheal prophylaxis consisting of high dose loperamide, given together with the combination of capecitabine plus neratinib for the first cycle of treatment in order to try to reduce the neratinib-related diarrhea. Among the 37 patients evaluable for safety, 32% of the patients had grade 3 diarrhea and 41% had grade 2 diarrhea.

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 trastuzumab, or the CONTROL trial. The CONTROL trial is an international, open-label, Phase II study investigating the use of loperamide prophylaxis with or without other agents in the reduction of neratinib-associated diarrhea that has a primary endpoint of the incidence of grade 3 diarrhea. In the CONTROL 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. The trial initially tested high dose loperamide prophylaxis given for the first 2 cycles (56 days) of treatment (12 mg on days 1-14, 8 mg on days 15-56 and as needed thereafter). 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 Amendment 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 2017, interim results from the CONTROL trial were presented at the 2017 CTRC-AACR San Antonio Breast Cancer Symposium. The CONTROL trial was then expanded to include two additional cohorts. One cohort received the combination of loperamide and budesonide and the other cohort received the combination of loperamide plus colestipol. Budesonide is a locally acting corticosteroid that the Company believes targets the inflammation identified in a preclinical model of neratinib-induced diarrhea and colestipol is a bile acid sequestrant that the Company believes targets potential bile acid malabsorption that could result from such inflammation.

The interim analysis of the trial presented in the poster included a total of 137 patients who received neratinib plus loperamide prophylaxis, 64 patients who received neratinib plus loperamide prophylaxis for 2 cycles and budesonide for 1 cycle, and 120 patients who received neratinib plus loperamide prophylaxis for 1 cycle and colestipol for 1 cycle. The results of the trial showed that the incidence of grade 3 diarrhea for the 137 patients who received the loperamide prophylaxis was 30.7%. For the 137 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 137 patients who received loperamide prophylaxis, 20.4% discontinued neratinib due to diarrhea. For the 64 patients who received the combination of loperamide plus budesonide, the results of the trial showed that the incidence of grade 3 diarrhea was 26.6%. The median number of grade 3 diarrhea episodes per patient was 1 and the median cumulative duration of grade 3 diarrhea was 2 days. For the 64 patients who received loperamide plus budesonide prophylaxis, 10.9% discontinued neratinib due to diarrhea.

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For the 120 patients who received the combination of loperamide plus colestipol, the results of the trial showed that the incidence of grade 3 diarrhea was 10.8%. 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 120 patients who received loperamide plus colestipol prophylaxis, 1.7% discontinued neratinib due to diarrhea. Further information is provided in Table 1 below:

Table 1: Characteristics of Treatment-Emergent Diarrhea

Study	CONTROL			ExteNET
	Loperamide (n=137)	Loperamide + budesonide (n=64)	Loperamide + colestipol (n=120)	Loperamide prn (n=1408)
Diarrhea, %				
Any grade	79.6	86.0	66.7	95.4
Grade 1	24.8	25.0	30.0	22.9
Grade 2	24.1	34.4	25.8	32.5
Grade 3[a]	30.7	26.6	10.8	39.8
Grade 4	0	0	0	0.1
Median cumulative duration, days				
Any grade	14.0	24.0	16.0	59.0
Grade ≥2	5.0	6.0	3.5	10.0
Grade ≥3	3.0	2.0	3.0	5.0
Median diarrhea episodes/patient				
Any grade	2.0	9.0	2.5	8.0
Grade ≥2	2.0	3.0	1.0	3.0
Grade ≥3	1.0	1.0	1.0	2.0
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalization	1.5	0	0	1.4
Duration of neratinib treatment, months				
Median	11.5	11.9	3.7	11.6

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

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.

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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 ESMO 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 SUMMIT 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 or HER3 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 SUMMIT 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 2015, 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 separate 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.

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 basket trial. Interim results from this ongoing Phase II trial were presented at the 2017 American Association for Cancer Research Annual Meeting (AACR) during the plenary session of the meeting. All patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea. Included in the presentation were data on 141 patients enrolled in the neratinib monotherapy arm of the trial, including 124 patients with HER2 mutations and 17 patients with HER3 mutations. This included patients with 21 unique tumor types, with the most common being breast, lung, bladder and colorectal cancer. There were also 30 distinct HER2 and 12 distinct HER3 mutations observed among these patients, with the most frequent HER2 variants involving S310, L755, A755_G776insYVMA and V777.

In the HER2-mutant cohort, clinical responses were observed in tumors with S310, L755, V777, P780_Y781insGSP and A775_G776insYVMA mutations. When stratified by tumor type, responses were observed in patients with breast, cervical, biliary, salivary and non-small-cell lung cancers, which led to cohort expansions in these tumor types. No activity was observed in the HER3-mutant cohort. A more detailed presentation of the data is presented in Table 1 below

Table 1: SUMMIT Trial Efficacy Summary

			HER2^{mut}				HER3^{mut}
	HER2^{mut} Breast (n=25)	HER2^{mut} Bladder (n=16)	Lung (n=26)	HER2^{mut} Colorectal (n=12)	HER2^{mut} Biliary tract (n=9)	HER2^{mut} Cervical (n=5)	NOS (n=17)
ORR at week 8, n (%)	8 (32.0)	0 (0.0)	1 (3.8)	0 (0.0)	2 (22.2)	1 (20.0)	0 (0.0)
(95% CI)	(14.9—53.5)	(0.0—20.6)	(0.1—19.6)	(0.0—26.5)	(2.8—60.0)	(0.5—71.6)	(0.0—20.6)
Clinical benefit rate, n (%)	10 (40.0)	3 (18.8)	11 (42.3)	1 (8.3)	3 (33.3)	3 (60.0)	2 (11.8)
(95% CI)	(21.1—61.3)	(4.0—45.6)	(23.4—63.1)	(0.2—38.5)	(7.5—70.1)	(14.7—94.7)	(1.6—38.3)
Median PFS, months	3.5	1.8	5.5	1.8	2.8	20.1	1.7
(95% CI)	(1.9—4.3)	(1.7—3.5)	(2.7—10.9)	(1.4—1.9)	(0.5—3.7)	(0.5—NA)	(1.4—2.0)

The neratinib safety profile observed in the SUMMIT study is consistent with that observed previously in metastatic patients with HER2 amplified tumors. With anti-diarrheal prophylaxis and management, diarrhea was not a treatment-limiting side effect in SUMMIT. The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. For the 141 patients enrolled in the neratinib monotherapy arm with safety data

available, 31 patients (22%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for those patients was 2 days. 4 patients (2.8%) permanently discontinued neratinib due to diarrhea and 21 patients (14.9%) temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided.

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 28 member states of the EU, or Member States, 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 face 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 competitors include, but are not limited to, Genentech, Novartis, Roche, Boehringer Ingelheim, Takeda, Daiichi Sankyo and Seattle Genetics. None of these companies are developing their drugs for the extended adjuvant treatment of early stage HER2-positive breast cancer that has been previously treated with a trastuzumab-containing regimen. All of these competitors are developing their drugs for the treatment of metastatic HER2-positive breast cancer. We are an early stage company with a limited history of operations, sales, marketing and 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 if we are able to commercialize additional product candidates. 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

During 2017, in connection with FDA approval of NERLYNX, we hired a U.S. specialty sales force of approximately 85 sales specialists who are focused on promoting NERLYNX to oncologists. This sales force is supported by an experienced sales leadership team comprised of regional sales managers, and our experienced commercial team comprised of experienced professionals in marketing, access and reimbursement, managed markets, marketing research, commercial operations, and sales force planning and management. In addition, our commercial infrastructure includes capabilities in manufacturing, medical affairs, quality control, and compliance.

We launched NERLYNX in the United States in July 2017, and our focus is to establish NERLYNX as the first choice for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer

following adjuvant trastuzumab-based therapy.

In other markets outside of the United States in which NERLYNX may be approved, if any, we may choose to commercialize NERLYNX independently or by establishing one or more strategic alliances such as the ones we have established for commercializing NERLYNX in South East Asia, beginning with Australia, Singapore, Malaysia, Brunei and New Zealand, Israel and in greater China, including mainland China, Taiwan, Hong Kong and Macau.

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 patent for the use of neratinib in the extended adjuvant treatment of early stage HER2 positive breast cancer that has previously been treated with a trastuzumab containing regimen that expires in 2030. 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 below, up to five years of patent term extension potentially available in the United States under the Hatch-Waxman Amendments. In addition, eight to eleven 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 patentable. 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 require 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.

In-License Agreement

In August 2011, Former Puma entered into an agreement pursuant to which Pfizer, or Licensor, 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. 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 connection with the FDA approval of NERLYNX in July 2017, we triggered a one-time milestone payment.

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. When sublicensing 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.

Out-License Agreements

In November 2017 and January 2018, we entered into three exclusive license agreements with STA, Medison and CANbridge granting them the right to seek the regulatory approval and, if approved, commercialize NERLYNX in South East Asia, Israel and in greater China, respectively. Under each of the agreements, we are entitled to upfront and milestone payments throughout the term of the applicable agreement, as well as significant double-digit royalties calculated as a percentage of net sales of the licensed products in the respective territory. The description below provides a summary of our agreements with Specialised Therapeutics and CANbridge.

Specialised Therapeutics Agreement

On November 20, 2017, we entered into a license agreement, or the Specialised Therapeutics Agreement, with STA. Pursuant to the Specialised Therapeutics Agreement, we granted to STA, under certain of our intellectual property rights relating to neratinib, an exclusive (including with respect to us and our affiliates), sublicensable license to commercialize any pharmaceutical product containing neratinib in finished form, or, for purposes of this description, the Licensed Product, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer and HER2-positive metastatic breast cancer in Australia, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, New Zealand, Papua New Guinea, Philippines, Singapore, Thailand, Timor-Leste and Vietnam, or the STA Territory.

The Specialised Therapeutics Agreement sets forth the parties' respective obligations with respect to the development, commercialization and supply of the Licensed Product. Within the STA Territory, STA will be generally responsible for regulatory and commercialization activities, and we will be solely responsible for the manufacturing and supply of the Licensed Product under a supply agreement that will be entered into between the parties.

Pursuant to the Specialised Therapeutics Agreement, we are entitled to upfront and other milestone payments of up to $4.5 million, payable upon achievement of the milestone events specified in the Specialised Therapeutics Agreement. Furthermore, we are entitled to receive significant double digit royalties calculated as a percentage of net sales of Licensed Products in the STA Territory.

The term of the Specialised Therapeutics Agreement continues, on a country-by-country basis, until the later of (i) the expiration or abandonment of the last patent covering the Licensed Product or (ii) the earlier of (a) the date upon which sales of generic versions of Licensed Product reach a specified level in such country, or (b) the tenth anniversary of the first commercial sale of the Licensed Product in such country. The Specialised Therapeutics Agreement may be terminated by either party if the other party commits a material breach, subject to a customary cure period, or if the other party is insolvent. The Specialised Therapeutics Agreement will also terminate upon the termination of the supply agreement for Licensed Products between the parties.

CANbridge Agreement

On January 30, 2018, we entered into an exclusive license agreement, or the CANbridge Agreement, with CANbridge. Pursuant to the CANbridge Agreement, we granted to CANbridge, under certain of our intellectual property rights relating to neratinib, an exclusive, sublicensable (under certain circumstances) license to develop and commercialize any pharmaceutical product containing neratinib, or, for purposes of this description, the Licensed Product, for the treatment of human disease, or for purposes of this description, the Field, in the People's Republic of China, or the CANbridge Territory, including mainland China, Hong Kong, Macao, and Taiwan, or, each, a CANbridge Region.

The CANbridge Agreement sets forth the parties' respective obligations with respect to the development, commercialization and supply of the Licensed Product. CANbridge will, at its expense, develop the Licensed Product for the purpose of obtaining regulatory approval in the Field and in the CANbridge Territory, subject to our approval of certain aspects of clinical studies conducted by CANbridge. Within the CANbridge Territory, CANbridge will be solely responsible, at its expense, for regulatory and commercialization activities. We will be solely responsible, subject to certain exceptions, for the manufacturing and supply of the Licensed Product under a supply agreement that will be entered into between the parties.

Pursuant to the CANbridge Agreement, we will receive an upfront payment of $30 million and potentially receive regulatory milestone payments totaling up to $40 million and sales-based milestone payments totaling up to $185 million. In addition, we are entitled to receive significant double-digit royalties calculated as a percentage of net sales of the Licensed Products in the CANbridge Territory.

The term of the CANbridge Agreement continues, on a CANbridge Region-by-CANbridge Region basis, until (i) the later of the expiration or abandonment of the last licensed patent covering the Licensed Product in such CANbridge Region or (ii) the earlier of (x) the date upon which sales of generic versions of the Licensed Product reach a specified level in such CANbridge Region, or (y) the tenth anniversary of the first commercial sale of the Licensed Product in such CANbridge Region. The CANbridge Agreement may be terminated by either party if the other party commits a material breach, subject to a customary cure period, or if the other party is insolvent; provided that if CANbridge materially breaches its development or commercialization obligations in a particular CANbridge Region, we may terminate the CANbridge Agreement solely with respect to such CANbridge Region. CANbridge may terminate the agreement at its convenience.

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 submission 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 with 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 substantial 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 August 2017, the Food and Drug Administration Reauthorization Act, or FDARA, was signed into law. Among other things, FDARA reauthorizes the FDA’s authority to collect user fees from industry participants to fund reviews of marketing applications for new 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 of the 60-day filing date, if the drug is a new molecular entity, 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 attempt 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 complete 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 approval, 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 representing 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 clinical 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 established by the Food and Drug Administration Safety and Innovation Act, or 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 clinical 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 breakthrough 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. 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 quicker 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 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 United 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 for 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 where 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 provides 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 approval 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 reference 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 Member States of the EU 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 the 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 NERLYNX and any other 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 current presidential administration and U.S. Congress will likely continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. Most recently, the Tax Cuts and Jobs Act was enacted, which, among other things, removes penalties for not complying with the Affordable Care Act's individual mandate to carry health insurance. 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. For example, the Budget Control Act of 2011, among other things, included 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 to the statute, will remain in effect through 2025 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of 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. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. 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 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 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.

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 commercialization of NERLYNX and 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 our products in clinical trials and commercial quantities. 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 2018 to further support the commercial launch of the drug.

Should any of our other 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 federal transparency requirements 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 and 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 $207.8 million for the year ended December 31, 2017, $222.8 million for the year ended December 31, 2016 and $208.5 million for the year ended December 31, 2015.

Employees

As of December 31, 2017, we had 318 employees, all of whom are full-time employees. In 2017, we hired 125 full-time employees for sales, marketing and other commercial product launch activities related to NERLYNX. We believe our relations with our employees are good. Over the course of the next year, we anticipate hiring up to 6 full-time employees devoted to clinical activities, 8 full-time employees for medical affairs, 8 full-time employees for the regulatory and quality assurance function, 4 full-time employees for logistics and distribution, 10 full-time employees for sales, marketing and commercial related activities, and 2 full-time employees for general and administrative 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 assets 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. Our business, financial condition, liquidity or results of operations could be materially adversely affected by any of these risks. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us.

Risks Related to our Business

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

We have a limited operating history, and, until recently, we have focused our efforts and resources primarily on obtaining regulatory approval for NERLYNX (neratinib) and on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel. On July 17, 2017, the FDA approved our first product, NERLYNX, for the extended adjuvant treatment of early stage, HER2-positive breast cancer in the United States, which became commercially available in the United States on July 31, 2017. We have a history of operating losses with net losses of $292.0 million for the fiscal year ended December 31, 2017 and $276.0 million and $239.3 million for the fiscal years ended December 31, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of approximately $1,088.5 million.

Although we received FDA approval and commenced commercialization of NERLYNX in the United States, we expect to incur substantial losses for the foreseeable future and may never become profitable. Moreover, even if we succeed in developing and commercializing one or more of other drug candidates, we may never become profitable. The successful development and commercialization of any drug candidate 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. As a result, we expect our losses to continue for the foreseeable future. Accordingly, we cannot assure you that we will achieve profitability in the future or that, if we do become profitable, we will sustain profitability. Our failure to achieve or maintain profitability could negatively impact the value of our common stock.

Our success depends on our ability to successfully commercialize NERLYNX. We are currently a single product company with limited commercial sales experience, which makes it difficult to evaluate our current business, predict our future prospects and forecast our financial performance and growth.

We have invested a significant portion of our efforts and financial resources in the development and commercialization of our lead product, NERLYNX, which was approved by the FDA for the extended adjuvant treatment of early stage, HER2-positive breast cancer in the United States on July 17, 2017, and we expect NERLYNX to constitute the vast majority of our product revenue for the foreseeable future. Our success depends on our ability to effectively commercialize NERLYNX. Successful commercialization of NERLYNX is subject to many risks. We have never, as an organization, launched or commercialized a product, and there is no guarantee that we will be able to do so successfully with NERLYNX. There are numerous examples of unsuccessful product launches and

failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than we have. The commercial success of NERLYNX depends on the extent to which patients and physicians accept and adopt NERLYNX. For example, if the expected patient population is smaller than we estimate or if physicians are unwilling to prescribe or patients are unwilling to take NERLYNX due to the related side effects, including diarrhea, the commercial potential of NERLYNX will be limited. Thus, significant uncertainty remains regarding the commercial potential of NERLYNX. Moreover, our ability to effectively generate product revenue from NERLYNX will depend on our ability to, among other things:

- achieve and maintain compliance with regulatory requirements;
- create market demand for and achieve market acceptance of NERLYNX through our marketing and sales activities and other arrangements established for the promotion of NERLYNX;

- compete with other breast cancer drugs (either in the present or in the future);
- train, deploy and support a qualified sales force;
- secure formulary approvals for NERLYNX at a substantial number of targeted hospitals;
- ensure that our third-party manufacturers manufacture NERLYNX in sufficient quantities, in compliance with requirements of the FDA and similar foreign regulatory agencies, if NERLYNX is approved by such foreign regulatory agencies, and at acceptable quality and pricing levels in order to meet commercial demand;
- ensure that our third-party manufacturers develop, validate and maintain commercially viable manufacturing processes that are compliant with current Good Manufacturing Practice, or cGMP, regulations;
- implement and maintain agreements with wholesalers, distributors and group purchasing organizations on commercially reasonable terms;
- ensure that our entire supply chain efficiently and consistently delivers NERLYNX to our customers;
- receive adequate levels of coverage and reimbursement for NERLYNX from commercial health plans and governmental health programs;
- provide co-pay assistance to help qualified patients with out-of-pocket costs associated with their NERLYNX prescription and/or other programs to ensure patient access to our products;
- educate physicians and patients about the benefits, administration and use of NERLYNX;
- obtain acceptance of NERLYNX as safe and effective by patients and the medical community;
- influence the nature of publicity related to our product relative to the publicity related to our competitors' products;
- obtain regulatory approvals for additional indications for the use of NERLYNX; and
- maintain and defend our patent protection and regulatory exclusivity for NERLYNX and to comply with our obligations under, and otherwise maintain, our intellectual property license with Pfizer and our license agreements with third parties.

Any disruption in our ability to generate product revenue from the sale of NERLYNX will have a material and adverse impact on our results of operations.

We have limited experience as a company in marketing or distributing pharmaceutical products. If we are unable to expand our marketing capabilities and effectively commercialize NERLYNX, our business, results of operations and financial condition may be materially adversely affected.

Our strategy is to build our sales, marketing and distribution capabilities to successfully commercialize NERLYNX in the United States. While we are continuing to establish our commercial team and hire our U.S. sales force, we have limited experience commercializing pharmaceutical products as an organization. In order to successfully market NERLYNX, we must continue to build our sales, marketing, managerial, compliance, and related capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing, and distribution capabilities, whether independently or with third parties, we may not be able to appropriately commercialize NERLYNX and may not become profitable.

Included in our strategy in the United States is a direct sales force to commercialize NERLYNX. These efforts will continue to be expensive and time-consuming, and we cannot be certain that we will be able to successfully develop this capability. NERLYNX is a newly-marketed drug and, therefore, none of the members of our sales force has ever promoted NERLYNX prior to its commercial launch. In addition, we must train our sales force to ensure that a consistent and appropriate message about NERLYNX is being delivered to our potential customers. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate potential customers about the benefits of NERLYNX and its proper administration, our efforts to successfully commercialize NERLYNX could be harmed, which would negatively impact our ability to generate product revenue.

Additionally, we will need to maintain and further develop our sales force to achieve commercial success, and we will be competing with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and

sales personnel. In the event we are unable to continue to develop and effectively maintain our commercial team, including our U.S. sales force, our ability to successfully commercialize NERLYNX would be limited, and we would not be able to generate product revenue successfully.

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 are subject to numerous risks, including:

- the expense and time required to recruit and train a sales force;
- 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 product;
- 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 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 products.

We may not be able to secure additional financing on favorable terms, or at all, to meet our future capital needs and our failure to obtain additional financing when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development or commercialization efforts or other operations.

Our operations have consumed substantial amounts of cash since inception. We expect our costs and expenses to increase in the future as we commercialize NERLYNX, including the cost of a direct sales force and the cost of manufacturing. We will also continue to expend substantial amounts on research and development of our other product candidates, including conducting clinical trials. Our future capital requirements will depend on many factors, including:

- the costs and expenses of our U.S. sales and marketing infrastructure, and of manufacturing;
- the degree of success we experience in commercializing NERLYNX;
- the revenue generated by the sale of NERLYNX and any other products that may be approved;
- the costs, timing and outcomes of clinical trials and regulatory reviews associated with our other product candidates;
- the emergence of competing products;
- the extent to which NERLYNX is adopted by the physician community and patients;
- the number and types of future products we develop and commercialize;
- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims;
- the costs of operating as a public company and compliance with existing and future regulations; and
- the extent and scope of our general and administrative expenses.

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 operations and successfully commercialize NERLYNX. The Company entered into a loan agreement with Silicon Valley Bank, or SVB, and Oxford Finance LLC, or Oxford, for a term loan of up to $100 million, subject to funding in two tranches. The Company received gross proceeds of $50 million from the first tranche of the credit facility upon closing on October 31, 2017 and intends to use the funds for general corporate purposes and to further support NERLYNX commercial initiatives. The second tranche of $50 million may be drawn at the Company's option subject to the achievement of certain revenue milestones. The loan will mature on October 31, 2022. 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. Additional financing may not be available on a timely basis on terms acceptable to us, or at all. We may raise funds in equity or debt financings to access funds for our capital needs. If we raise additional funds through further issuances of equity or convertible debt securities, our existing stockholders could suffer significant dilution in their percentage ownership of our company, and any new equity securities we issue could have rights, preferences and privileges senior to those of holders of our common stock. Any debt financing obtained by us in the future would cause us to incur debt service expenses and could include restrictive covenants relating to our capital raising activities and other financial and operational matters, which may make it more difficult for us to obtain additional capital and pursue business opportunities. If we are unable to obtain adequate financing or financing on terms satisfactory to us when we require it, we may terminate or delay the development of one or more of our product candidates, delay clinical trials necessary to market our products, or delay establishment of sales and marketing capabilities or other activities necessary to commercialize our products. If this were to occur, our ability to continue to grow and support our business and to respond to business challenges could be significantly limited. Furthermore, 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. Additionally, even though we have commenced the commercialization of NERLYNX, we will need to maintain and further develop our sales force to achieve commercial success, and we will be competing with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. In the event we are unable to continue to develop and effectively maintain our commercial team, including our U.S. sales force, our ability to successfully commercialize NERLYNX would be limited, and we would not be able to generate product revenue successfully. 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.

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, 2017 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.

The terms of our credit facility place restrictions on our ability to operate our business and on our financial flexibility, and we may be unable to achieve the revenue necessary for us to incur additional borrowings under the credit facility or to satisfy the minimum revenue covenants.

The terms of our credit facility place restrictions on our ability to operate our business and our financial flexibility. On October 31, 2017, we entered into a loan and security agreement, which we refer to as the credit facility, with SVB as administrative and collateral agent, and the lenders party thereto from time to time, including SVB and Oxford pursuant to which the lenders agreed to make term loans available to us in an aggregate amount of $100 million, consisting of (i) a Term Loan A in an aggregate amount of $50 million available on the effective date and (ii) a Term Loan B in an aggregate amount of $50 million available to be drawn at our option between March 31, 2018 and June 30, 2018 provided we have achieved a specified minimum revenue milestone and no event of default is occurring. As of December 31, 2017, we had $50 million in principal outstanding under the credit facility. We cannot assure you that we will achieve the revenue milestone that will trigger our ability to draw the Term Loan B, and accordingly, we may never be able to borrow the additional $50 million provided for in the credit facility. The credit facility is secured by substantially all of our personal property, other than our intellectual property.

The credit facility includes affirmative and negative covenants applicable to us, our current subsidiary and any subsidiaries we create in the future. The affirmative covenants include, among others, covenants requiring us to maintain our legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage and satisfy certain requirements regarding deposit accounts. We must also achieve product revenue, measured as of the last day of each fiscal quarter on a trailing 3-month basis, that is (i) greater than or equal to 70% of the revenue target set forth in our board-approved projections for the 2017 fiscal year, (ii) greater than or equal to 50% of the revenue target set forth in our board-approved projections for the 2018 fiscal year, and (iii) greater than or equal to 50% of the revenue target set forth in our board-approved projections for the 2019 fiscal year. New minimum revenue levels will be established for each subsequent fiscal year by mutual agreement of us, SVB as administrative agent, and the lenders. The negative covenants include, among others, restrictions on us transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, making investments, creating liens, selling assets and suffering a change in control, in each case subject to certain exceptions. These covenants may make it difficult for us to operate our business. In addition, we are in the early stages of commercializing NERLYNX and we cannot assure you that we will be able to achieve the minimum revenue requirements provided for in the credit facility. Our failure to satisfy the revenue, or any other, covenant could result in an event of default under the loan.

The credit facility also includes events of default, the occurrence and continuation of which could cause interest to be charged at the rate that is otherwise applicable plus 5% and would provide SVB, as collateral agent, with the right to exercise remedies against us and the collateral securing the credit facility, including foreclosure against the property securing the credit facilities, including our cash. These events of default include, among other things, our failure to pay principal or interest due under the credit facility, a breach of certain covenants under the credit facility, our insolvency, a material adverse change, the occurrence of any default under certain other indebtedness in an amount greater than $500,000 and one or more judgments against us in an amount greater than $500,000 individually or in the aggregate.

NERLYNX or our other drug candidates 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, as applicable.

Undesirable side effects caused by NERLYNX or our other 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 NERLYNX 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 clinical trials or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Additionally, if we or others later identify undesirable side effects caused by any approved product, 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 NERLYNX or the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Even though the FDA has granted approval of NERLYNX for the extended adjuvant treatment of early stage, HER2-positive breast cancer, the terms of the approval may limit its commercial potential.

Even though the FDA has granted approval of NERLYNX, the scope and terms of the approval may limit our ability to commercialize NERLYNX and, therefore, our ability to generate substantial sales revenue. The FDA has approved NERLYNX only for the extended adjuvant treatment of early stage, HER2-positive breast cancer. In connection with the FDA approval, we have committed to conduct the following post-marketing studies: (i) a physiologically-based pharmacokinetic, or PBPK, modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the potential for excessive drug toxicity, or if the PBPK modeling/simulation is not feasible, a clinical pharmacokinetic trial, (ii) a PBPK modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations, (iii) a clinical pharmacokinetic trial to evaluate whether separating the dosing of H2-receptor antagonists and neratinib can minimize the drug-drug interaction potential, (iv) the submission of the final results of our 2-year carcinogenicity study in the rat, and (v) submission of certain trial data from our ongoing clinical trials. If we fail to comply with our post-marketing commitments, or if the results of the post-marketing studies, or any other ongoing clinical studies of NERLYNX, are negative, the FDA could decide to withdraw approval, add warnings or narrow the approved indication in the product label.

We are heavily dependent on the success of NERLYNX, which is still under clinical development for various additional indications. While the FDA has approved NERLYNX for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer, we cannot be certain that NERLYNX will receive regulatory approval for any other indication for which we may seek approval.

The FDA has approved NERLYNX only for the extended adjuvant treatment of early stage, HER2-positive breast cancer in adult patients following adjuvant trastuzumab-based therapy. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to the development of NERLYNX in various additional indications. Accordingly, our business currently depends heavily on the successful development and regulatory approval of NERLYNX for additional indications. 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 NERLYNX for other indications or any of our other drug candidates in the United States until we receive approval of an NDA from the FDA for such indications, or, in any foreign countries, until requisite approval from such countries. In June 2016, we submitted an MAA with the EMA. In August 2017, the Committee for Medicinal Products for Human Use of the EMA, or CHMP, issued its Day-180 List of Outstanding Issues in the process of their ongoing regulatory review of the MAA, requesting additional data analyses related to the safety and efficacy of neratinib and instituting a clock stop in order to allow the Company time to respond to this List of Outstanding Issues. The Company responded to the list in December 2017. The CHMP recently recommended refusal of our MAA for neratinib for the extended adjuvant treatment of early stage HER2-positive breast cancer but allowed us to request a re-examination which we intend to do.

Approval of NERLYNX by the FDA for the extended adjuvant treatment of early stage, HER2-positive breast cancer in adult patients following adjuvant trastuzumab-based therapy does not ensure that a foreign jurisdiction will also approve NERLYNX for that indication, nor does it ensure that NERLYNX will be approved by the FDA for any other

indications. Obtaining approval of an NDA or foreign marketing application is an extensive, lengthy, expensive and inherently uncertain process, and the FDA or a foreign regulator may delay, limit or deny approval of a drug candidate for many reasons, including:

- we may not be able to demonstrate that NERLYNX or any other drug candidate is safe and effective as a treatment for our targeted indications to the satisfaction of the FDA or other regulator;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or other regulator for marketing approval;
- the FDA or other regulator 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 or other regulator may not find the data from pre-clinical studies and clinical trials sufficient to demonstrate that the clinical and other benefits of NERLYNX or any other drug candidate outweigh the safety risks;
- the FDA or other regulator 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 or other regulator 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 or other regulator may identify deficiencies in the manufacturing processes or facilities of our third-party manufacturers; or
- the FDA or other regulator may change its approval policies or adopt new regulations.

If we do not obtain regulatory approval of NERLYNX for other indications in the United States, or for any indication in foreign jurisdictions, we will not be able to market NERLYNX for other indications or in other jurisdictions, which will limit our commercial revenue.

We have no experience in drug formulation or manufacturing and plan to rely exclusively on third parties to formulate and manufacture NERLYNX and our drug candidates, and any disruption or loss of these relationships could delay our development and commercialization efforts.

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 NERLYNX and our 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 and the commercialization of NERLYNX. If we are unable to continue our relationships with one or more of these third-party contractors, we could experience delays in our development or commercialization efforts as we locate and qualify new manufacturers. 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.
- 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 and/or commercial needs.
- 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 for commercialization, as applicable.
- The facilities used by our contract manufacturers to manufacture NERLYNX and our other 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 cGMP regulations 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 our other drug candidates, if approved, or market NERLYNX.

- 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 NERLYNX or our other drug candidates, or result in higher costs or deprive us of potential product revenue.

If our third-party manufacturers fail to manufacture NERLYNX in sufficient quantities and at acceptable quality and pricing levels, or fail to fully comply with cGMP regulations, we may face delays in commercialization or be unable to meet market demand, and may lose potential revenues.

The manufacture of NERLYNX requires significant expertise and capital investment, including the development of advanced manufacturing techniques, process controls and the use of specialized processing equipment. Our third-party manufacturers must comply with federal, state and foreign regulations, including the FDA's regulations governing cGMP, enforced by the FDA through its facilities inspection program and by similar regulatory authorities in other jurisdictions where we do business. These requirements include, among other things, quality control, quality assurance and the maintenance of records and documentation. The FDA or similar foreign regulatory authorities at any time may implement new standards, or change their interpretation and enforcement of existing standards for manufacture, packaging or testing of our products. Any failure by us or our third-party manufacturers to comply with applicable regulations may result in fines and civil penalties, suspension of production, product seizure or recall, operating restrictions, imposition of a consent decree, modification or withdrawal of product approval or criminal prosecution and would limit the availability of our product. Any manufacturing defect or error discovered after products have been produced and distributed also could result in significant consequences, including costly recall procedures, re-stocking costs, damage to our reputation and potential for product liability claims.

If our third-party manufacturers are unable to produce the required commercial quantities of NERLYNX to meet market demand for NERLYNX on a timely basis or at all, or if they fail to comply with applicable laws for the manufacturing of NERLYNX, we will suffer damage to our reputation and commercial prospects and we will lose potential revenue.

We are substantially dependent on international third-party licensees for the development and commercialization of NERLYNX in several countries outside the United States. The failure of these licensees to meet their contractual, regulatory, and other obligations could adversely affect our business.

We have entered into exclusive license agreements with several third parties that provide these licensees exclusive rights to the development and commercialization of NERLYNX in South East Asia, Israel and greater China. As a result, we are entirely dependent on these parties to achieve regulatory approval of NERLYNX for marketing in these countries and for the commercialization of NERLYNX, if approved. The timing and amount of any milestone and royalty payments we may receive under these agreements, as well as the commercial success of NERLYNX, will depend on, among other things, the efforts, allocation of resources and successful commercialization of NERLYNX by the licensees. We also depend on these third parties to comply with all applicable laws relative the development and commercialization of our products in those countries. We do not control the individual efforts of these licensees and have limited ability to terminate these agreements if the licensees do not perform as anticipated. The failure of these licensees to devote sufficient time and effort to the development and commercialization of NERLYNX, or the failure of these licensees to meet their obligations to us, including for future royalty and milestone payments; to adequately deploy business continuity plans in the event of a crisis; and/or satisfactorily resolve significant disagreements with us or address other factors, could have an adverse impact on our financial results and operations. In addition, if these third parties violate, or are alleged to have violated, any laws or regulations during the performance of their obligations for us, it is possible that we could suffer financial and reputational harm or other negative outcomes, including possible legal consequences.

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

Although the FDA approved NERLYNX for the extended adjuvant treatment of early stage, HER2-positive breast cancer in the United States on July 17, 2017, NERLYNX is still under development for various indications, and our other drug candidates are in development as well, all of which will require extensive clinical testing before we can submit any NDA for regulatory approval. We cannot predict with any certainty that 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 drug candidates may not be predictive of the results of later-stage clinical trials. Drug 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, foreign regulatory authorities, 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 or such other regulator finds deficiencies in our IND or comparable 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 revenue 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 revenue. 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 revenue.

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While we have negotiated a Special Protocol Assessment, or SPA, 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 an 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.

Planned expansion into new markets outside of the United States will subject us to additional business and regulatory risks, and there can be no assurance that our products will be accepted in those markets.

We recently entered into exclusive license agreement with third parties to pursue regulatory approval and commercialize NERLYNX, if approved, in South East Asia, Israel and greater China. We plan to continue to pursue commercialization of NERLYNX in other countries outside the United States, if approved. Engaging in international business inherently involves a number of difficulties and risks, including:

- competition from established companies, many of which are well-positioned within their local markets with longer operating histories, more recognizable names and better established distribution networks;
- the availability and level of coverage and reimbursement within prevailing foreign healthcare payment systems and the ability of patients to elect to privately pay for NERLYNX and our other products, if approved;

- difficulties in enforcing intellectual property rights;
- pricing pressure;
- required compliance with existing and changing foreign regulatory requirements and laws;
- laws and business practices favoring local companies;
- longer sales and payment cycles;
- difficulties in enforcing agreements and collecting receivables through certain foreign legal systems;
- political and economic instability;
- foreign currency risks that could adversely affect our financial results;
- potentially adverse tax consequences, tariffs and other trade barriers;

- exposure to liabilities under anti-corruption and anti-money laundering laws, including the U.S. Foreign Corrupt Practices Act, or FCPA, and similar laws and regulations in other jurisdictions;
- international terrorism and anti-American sentiment;
- difficulties and costs associated with staffing and managing foreign operations; and
- export restrictions and controls relating to technology.

If we or our third party manufacturers are unable to address these international risks, we may fail to establish and maintain an international presence, and our business, financial condition and results of operations would suffer.

The failure to comply with anti-bribery, anti-corruption, and anti-money laundering laws, including the FCPA and similar laws associated with our activities outside of the United States, could subject us to penalties and other adverse consequences.

We are subject to the FCPA, regulations of the U.S. Office of Foreign Assets Control, the United Kingdom Bribery Act of 2010 and other anti-corruption, anti-bribery and anti-money laundering laws around the world where we conduct activities, including, if approved in such countries, the sale of NERLYNX. We face significant risks and liability if we fail to comply with the FCPA and other anti-corruption and anti-bribery laws that prohibit companies and their employees and third-party business partners, such as distributors or resellers, from authorizing, offering or providing, directly or indirectly, improper payments or benefits to foreign government officials, political parties or candidates, employees of public international organizations including healthcare professionals, or private-sector recipients for the corrupt purpose of obtaining or retaining business, directing business to any person, or securing any advantage. We currently rely on various third parties for certain services outside the United States, including continued development of NERLYNX and, if approved, its subsequent commercialization. We may be held liable for the corrupt or other illegal activities of these third parties and intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize such activities.

Any violation of the FCPA, other applicable anti-bribery, anti-corruption laws, and anti-money laundering laws could result in whistleblower, adverse media coverage, investigations, loss of export privileges, severe criminal or civil sanctions and, in the case of the FCPA, suspension or debarment from U.S. government contracts, which could have a material and adverse effect on our reputation, business, operating results and prospects. In addition, responding to any enforcement action or related investigation may result in a materially significant diversion of management's attention and resources and significant defense costs and other professional fees.

If we fail to comply with United States export control and economic sanctions or fail to expand and maintain an effective sales force or successfully develop our international distribution network, our business, financial condition and operating results may be adversely affected.

When selling any products outside of the United States, including NERLYNX, if approved for commercialization outside of the United States, we are subject to United States export control and economic sanctions laws, the violation of which could result in substantial penalties being imposed against us. More broadly, if we fail to comply with export control laws, any sales could fail to grow or could decline, and our ability to grow our business could be adversely affected.

Regulatory approval for any approved product is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated as set forth on the product label. If we market NERLYNX for uses beyond such approved indications, we could be subject to enforcement action, which could have a material adverse effect on our business.

The FDA strictly regulates marketing, labeling, advertising and promotion of prescription drugs. These regulations include standards and restrictions for direct-to-consumer advertising, industry-sponsored scientific and educational activities, promotional activities involving the internet and off-label promotion. Any regulatory approval that the FDA grants is limited to those specific diseases and indications for which a product is deemed to be safe and effective by the FDA. For example, the FDA-approved label for NERLYNX is limited to the extended adjuvant treatment of adult patients with early stage, HER2-positive breast cancer following adjuvant trastuzumab-based therapy. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our drugs and drug candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians in the United States may choose, and are generally permitted, to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, our ability to promote the products is narrowly limited to those indications that are specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off-label use. Although recent court decisions suggest that certain off-label promotional activities may be protected under the First Amendment, the scope of any such protection is unclear. If our promotional activities fail to comply with the FDA's regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, bring an enforcement action against us, suspend or withdraw an approved product from the market, require a recall or institute fines or civil fines, or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our reputation and our business.

Even though the FDA has approved NERLYNX for the extended adjuvant treatment of early stage, HER2-positive breast cancer in adult patients following adjuvant trastuzumab-based therapy, we will be subject to ongoing obligations and continued regulatory review with regard to NERLYNX and any other drug candidates that receive FDA approval, which may result in significant additional expense. Additionally, NERLYNX and 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.

The FDA's approval of the NDA for NERLYNX and any regulatory approvals that we receive for our other drug 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, 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 drug 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 administrative 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 issuance 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, and review and approval of marketing applications. It is difficult to predict how these Executive Orders will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. 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.

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 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 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 drug candidates could be delayed.

Health care reform measures may hinder or prevent our products' and product 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 product and product candidates, 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.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA. As a result, there have been delays in the implementation of, and action taken to repeal or replace, certain aspects of the ACA. We expect that the Trump administration and U.S. Congress will continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. 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. For example, the Budget Control Act of 2011 resulted in 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, the American Taxpayer Relief Act of 2012, 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 been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in 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 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 which future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

We anticipate that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and 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. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product and product candidates, if approved.

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Failure to obtain or maintain adequate coverage and reimbursement for our products or product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

Successful commercial sales of any approved products will depend on the availability of adequate coverage and reimbursement from government health administration authorities, private health insurers and other third-party payors. Each third-party payor separately decides which products it will cover and establishes the reimbursement level, and there is no guarantee that any of our approved products or product candidates that may be approved for marketing by regulatory authorities will receive adequate coverage or reimbursement levels. Obtaining and maintaining coverage approval for a product is time-consuming, costly and may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of coverage and reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or limited, we may not be able to successfully commercialize any product or product candidate for which we obtain marketing approval. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for drugs and biologics. Even if we obtain coverage for a given product, the resulting reimbursement rates may be inadequate and may affect the demand for, or the price of, any product candidate for which we obtain marketing approval.

We expect to experience pricing pressures in connection with the sale of NERLYNX (oral), NERLYNX (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 are subject, directly and indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws and health information privacy and security laws. Failure to comply with these laws may subject us to substantial penalties.

We do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors. However, federal and state healthcare laws and regulations pertaining to fraud and abuse, physician payment transparency, privacy and security laws and regulations may apply to us depending on programs we operate and have been asserted by the government and others to apply to companies like us, and our arrangements with healthcare providers, customers and other entities, including our marketing practices, educational programs and pricing policies. These laws include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, 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 fraudulent claim for purposes of the False Claims Act;
- federal false claims laws, including, without limitation, the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal third-party payors that are false or fraudulent, such as engaging in improper promotion of products or submitting inaccurate price reports to the Medicaid Drug Rebate program;
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the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary's decision to order or receive items or services reimbursable by the government from a particular provider or supplier;

- federal criminal laws that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information held by certain covered entities and their business associates, and imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to Centers for Medicare & Medicaid Services, or CMS, information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians described above and their immediate family members and payments or other "transfers of value" to such physician owners (manufacturers are required to submit reports to CMS by the 90th day of each calendar year);
- analogous state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and pricing information; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under such laws, it is possible that some of our business activities, including our relationships with physicians and other healthcare providers, some of whom recommend, purchase and/or prescribe our products, and the manner in which we promote our products, could be subject to challenge under one or more of such laws.

We are also exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and agents may engage in fraudulent or other illegal activity. While we have policies and procedures in place prohibiting such activity, misconduct by these parties could include, among other infractions or violations, intentional, reckless and/or negligent conduct or unauthorized activity that violates FDA requirements, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, laws that require the true, complete and accurate reporting of financial information or data or other commercial or regulatory laws or requirements. It is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations.

If our operations are found to violate any of the laws described above or any other laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment of officers involved, any of which could adversely affect our ability to market our current and any future products, once approved, and materially adversely affect our business, results of operations and financial condition. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by CMS, and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors

in connection with drugs, including NERLYNX, that are dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The terms, scope and complexity of these government pricing programs change frequently. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming.

In addition, there is increased focus by the Office of Inspector General on the methodologies used by manufacturers to calculate average manufacturer price, or AMP, and best price, or BP, to assess manufacturer compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty per day for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In the event that CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

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 drugs and drug candidates is characterized by intense competition and rapid technological advances. NERLYNX competes, and any of our other drug candidates that receives FDA approval 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 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.

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, 2017, we had 318 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, 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 potential 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 other 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, such parties could bring legal action against us or our licensors or collaborators 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 the 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 convincing 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.

We cannot predict the extent to which investor interest in our company will be sufficient to maintain an active trading market on the NASDAQ Global Select Market 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, 2017, we estimate that our officers, directors and their affiliated entities, and our 5% or greater stockholders, collectively beneficially owned approximately 70.8% of our outstanding shares of common stock. 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:

- our ability to successfully commercialize NERLYNX in the United States for the extended adjuvant treatment of early stage, HER2-positive breast cancer;
- the status and cost of our marketing commitments for NERLYNX;
- the status and cost of development and commercialization of neratinib for indications other than in the treatment of HER2-positive breast cancer and in jurisdictions other than in the United States, if approved;
- 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 analyst 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. In addition, we and certain of our executive officers have been named as defendants in a securities class action and derivative lawsuits captioned Hsu vs. Puma Biotechnology, Inc., et al., Xing Xie vs. Alan H. Auerbach, and Kevin McKenney vs. Auerbach. 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 these 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 securities class action and derivative lawsuits.

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 price 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 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 publishing, research 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, and the payment of dividends is also restricted under our credit facility. 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 space 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 or the “plaintiff,” individually and on behalf of all others similarly situated, filed a class action lawsuit against us or “the defendants” 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 a consolidated complaint on behalf of all persons who purchased our securities between July 22, 2014 and May 29, 2015. The consolidated complaint alleges that we and certain of our executive officers made false 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 September 30, 2016, the court denied the defendants’ motion to dismiss the consolidated complaint. On June 6, 2017, the lead plaintiff filed a first amended complaint that included new claims about additional statements that plaintiff alleges are false or misleading. On June 19, 2017, the defendants moved to dismiss the new claims in the amended complaint. On July 25, 2017, the court denied the motion to dismiss. On December 8, 2017, the court granted the plaintiff’s motion for class certification. A trial date is currently set for November 6, 2018. We intend to vigorously defend against 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. Discovery ended in September 2017. Summary judgment briefing was completed on November 17, 2017. It is unknown when the court will rule on the summary judgment motions. We intend to vigorously defend against Dr. Eshelman’s claims.

Derivative Actions

On April 12 and April 14, 2016, alleged shareholders filed two derivative lawsuits purportedly on behalf of us against certain of our officers and directors in the Superior Court of the State of California, Los Angeles, captioned Xing Xie vs. Alan H. Auerbach, No. BC616617, and Kevin McKenney vs. Auerbach, 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 securities class action described above. The complaints seek an unspecified sum of damages and equitable relief. These two derivative claims are currently stayed, pending the outcome of the Hsu securities class action. We intend to vigorously defend against this matter.

Separately, on February 9, 2018, another alleged shareholder filed a derivative lawsuit purportedly on behalf of us against certain of our officers and directors in the United States District Court, Central District of California, captions Arnaud Van Der Gracht De Rommerswael vs. Alan H. Auerbach, et al., No. 8:18-cv-00236. The complaint asserts claims for violation of securities law, breach of fiduciary duty, waste of corporate assets, and unjust enrichment arising from substantially similar allegations as those contained in the securities class action described above. The complaint seeks an unspecified sum of damages, corporate reforms, equitable relief, and restitution. We intend to vigorously defend against this matter.

Stockholder Demand

On September 13, 2017, a purported stockholder filed a complaint in the Court of Chancery of the State of Delaware seeking an equitable apportionment of attorneys' fees in an unspecified amount. The purported stockholder alleges that his actions caused our board of directors to implement certain governance reforms and enhancements to our director compensation program, and that, as a result of his actions, the purported stockholder is entitled to attorneys' fees in an amount commensurate to those purported benefits. We filed an answer to the complaint on October 20, 2017. We intend to vigorously defend against 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.

ITEM 4. MINE SAFETY DISCLOSURE
Not applicable.

PART II

ITEM 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 3, 2017. Prior to January 3, 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 NASDAQ in 2017 and on NYSE in 2016 are set forth below for the periods indicated:

2017	High	Low
First quarter	$45.44	$28.95
Second quarter	92.00	28.35
Third quarter	120.85	71.14
Fourth quarter	136.90	92.36

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

On February 20, 2018, the last reported sale price for our common stock on NASDAQ was $67.05 per share.

Record Holders

On February 20, 2018, we had 15 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 15,255 additional owners held our common stock in "Street Name" as of February 20, 2018.

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. Additionally, we are restricted from paying cash dividends under our credit facility with SVB.

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 2017.

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 2017.

Performance Graph

The graph below compares the cumulative total return of the Company's common stock from December 31, 2012, through December 31, 2017, with the cumulative total returns on (i) the Nasdaq Biotechnology Index and (ii) the Nasdaq Composite Index. The following indices were used in prior years and are presented for comparative purposes, but, since our common stock has been quoted on NASDAQ since January 3, 2017, we believe that the comparison to the Nasdaq Biotechnology Index and the Nasdaq Composite Index to be more meaningful; (i) the NYSE ARCA Biotechnology Index, (ii) the NYSE Healthcare Index and (iii) the NYSE Composite Index. The comparison assumes investment of $100 on December 31, 2012, in our common stock and in each index and, for each index, assumes reinvestment of all dividends.

The historical price performance included below is not necessarily indicative of future stock price performance.

The material in this performance graph is not soliciting material, is not deemed filed with the SEC and is not incorporated by reference in any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act, whether made on, before or after the date of this filing and irrespective of any general incorporation language in such filing.

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, 2017, 2016 and 2015 and the Consolidated Balance Sheet Data as of December 31, 2017 and 2016 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 years ended December 31, 2014 and 2013 and the Consolidated Balance Sheet Data as of December 31, 2015, 2014 and 2013 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,				
	2017	2016	2015	2014	2013
	(in millions, except share and per share data)				
Statement of Operations Data:					
Product revenue, net	$26.2	$—	$—	$—	$—
License revenue	1.5	—	—	—	—
Expenses:					
Cost of sales	5.6	—	—	—	—
Selling, general and administrative	106.7	53.8	31.8	19.4	9.8
Research and development	207.8	222.8	208.5	122.9	45.0
Operating loss	(292.4)	(276.6)	(240.3)	(142.3)	(54.8)
Interest income	1.2	1.0	1.0	0.3	0.2
Interest expense	(0.7)	—	—	—	—
Other income	(0.1)	(0.4)	—	—	—
Totals	0.4	0.6	1.0	0.3	0.2
Net loss	(292.0)	(276.0)	(239.3)	(142.0)	(54.6)
Net loss attributable to common stock	(292.0)	(276.0)	(239.3)	(142.0)	(54.6)
Net loss per common share—basic and diluted	$(7.85)	$(8.29)	$(7.45)	$(4.73)	$(1.90)
Weighted-average common shares outstanding—basic and diluted	37,169,678	33,295,114	32,126,094	30,010,979	28,696,573

	As of December 31,				
	2017	2016	2015	2014	2013
	(in millions)				
Balance Sheet Data:					
Total assets	$165.5	$252.8	$239.8	$162.8	$104.4
Total liabilities	112.2	43.0	33.8	45.7	20.4
Total stockholders' equity	53.3	209.8	206.0	117.0	84.0

	Years Ended December 31,				
	2017	2016	2015	2014	2013
	(in millions)				
Other Financial Data:					
Net cash used in operating activities	$(172.5)	$(141.7)	$(154.5)	$(77.2)	$(55.0)
Net cash (used in) provided by investing activities	(15.4)	142.2	(85.9)	(63.3)	(41.5)
Net cash provided by financing activities	75.1	162.4	233.4	136.0	2.2

Item 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 and commercialization 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. Prior to 2017, our efforts and resources to date had been focused primarily on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel. During 2017, the United States Food and Drug Administration, or FDA, approved NERLYNX, formally known as PB272 (neratinib(oral)), for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following trastuzumab-based therapy. Developing drug products, however, is a lengthy and very expensive process.

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 Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, in June 2016. We are continuing to evaluate potential commercialization options for NERLYNX outside the United States 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, we signed an amendment to the license agreement with the Licensor whereby we 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 begin to decline unless we decide to pursue additional clinical trials in alternate indications or acquire additional product candidates.

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, proceeds from our credit facility and sales of our common stock in private placements.

Summary of Income and Expenses

Product revenue, net

Product revenue, net consists of revenue from sales of NERLYNX. We record revenue at the net sales price, which includes an estimate for variable consideration for which reserves are established. Variable consideration consists of trade discounts and allowances, product returns, provider chargebacks and discounts, government rebates and other incentives.

License revenue

License revenue consists of consideration paid to us pursuant to our license agreements.

Cost of sales

Cost of sales consists of third-party manufacturing costs, freight, and indirect overhead costs associated with sales of NERLYNX. Cost of product sales may also include period costs related to royalty charges payable to the Licensor, the amortization of a milestone payment made to the Licensor after obtaining FDA approval of NERLYNX, certain inventory manufacturing services, inventory adjustment charges, unabsorbed manufacturing and overhead costs, and manufacturing variances.

Selling, general and administration expenses

Selling, general and administrative, or SG&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. Internal expenses primarily consist of payroll-related costs, but also include facilities and equipment costs, travel expenses and supplies. External expenses primarily consist of legal fees, insurance expenses and consulting for activities such as sales, marketing and software implementations to support corporate growth.

Research and development 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, 2017, 2016 and 2015, 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. Internal expenses primarily consist of payroll-related costs, but also include equipment costs, travel expenses and supplies. External expenses primarily consist of clinical trial expenses and consultant and contractor expense, but also include costs such as legal fees, insurance costs and manufacturing expense.

Results of Operations

The following summarizes our results of operations for the periods indicated.

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

Total revenue

Total revenue was approximately $27.7 million for the year ended December 31, 2017 compared to $0 for the year ended December 31, 2016.

Product revenue, net

Product revenue, net was approximately $26.2 million for the year ended December 31, 2017, compared to $0 for the year ended December 31, 2016. This increase in product revenue, net was entirely attributable to sales of NERLYNX, our initial product, following its commercial launch in July 2017.

License revenue

License revenue was approximately $1.5 million for the year ended December 31, 2017, compared to $0 for the year ended December 31, 2016. This increase in license revenue was entirely attributable to an upfront payment in an out-license agreement.

Cost of sales

Cost of sales was approximately $5.6 million for the year ended December 31, 2017, compared to $0 for the year ended December 31, 2016. The increase in cost of sales was entirely attributable to the commercial launch of NERLYNX, our initial product, in July 2017.

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

Total revenue

Total revenue was $0 for the years ended December 31, 2016 and 2015 as we did not generate revenue until the commercial launch of NERLYNX during 2017.

Cost of sales

Cost of sales was $0 for the years ended December 31, 2016 and 2015 because we did not yet have a commercial product.

Selling, general and administrative expenses:

Selling, general and administrative expenses (in thousands)	2017	2016	2015	Annual Percentage Change 2017/2016	2016/2015
External	$41,364	$14,172	$6,925	191.9%	104.6 %
Internal	34,135	13,003	7,717	162.5%	68.5 %
Employee stock-based compensation expense	31,194	26,623	17,166	17.2 %	55.1 %
	$106,693	$53,798	$31,808	98.3 %	69.1 %

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

Total SG&A expenses increased approximately 98.3% to $106.7 million for the year ended December 31, 2017 from $53.8 million for the year ended December 31, 2016. Approximately $16.1 million of this increase, or 30.4% of the total increase, is related to the hiring and training of a commercial sales force and field based support personnel (approximately 100 employees) upon obtaining FDA approval of NERLYNX. The remaining approximately $36.8 million increase in SG&A expense for the year ended December 31, 2017 compared to the same period in 2016 was primarily attributable to:

- an approximately $27.2 million increase in external costs for commercial launch and non-commercial launch related expenses primarily comprised of:
- an approximately $18.4 million increase in expenses related to the commercial launch of NERLYNX, primarily driven by an approximately $5.8 million increase in marketing, an approximately $5.4 million increase in system infrastructure, an approximately $4.3 million increase in patient programs and consulting and an approximately $2.9 million increase for recruiting and on-boarding costs of the sales force; and
- an approximately $8.8 million increase in non-launch related external expenses, primarily driven by an approximately $7.3 million increase in legal expenses and an approximately $1.5 million increase from various additional expenses such as audit fees, additional temporary labor and administrative fees to support overall corporate growth.
- an approximately $5.0 million additional increase in internal expenses. Included in this increase are an approximately $1.7 million increase in headcount in marketing and market access to support the commercial launch, an approximately $1.3 million increase in G&A headcount and an approximately $2.0 million increase of expense to support corporate growth in the form of increased software and depreciation expenses; and
- an increase of approximately $4.6 million in employee stock-based compensation for employees hired during 2017 and annual awards to existing employees.

We expect SG&A expenses to increase in 2018. The majority of the salesforce and field based support personnel were hired in the late 3rd quarter of 2017 while we expect a full years' worth of sales force expenses in 2018. This increase should only be partially offset by an expected reduction in legal fees and system implementation fees.

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

Total SG&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 SG&A expense for the year ended December 31, 2016 compared to the same period in 2015 was primarily attributable to:

- an approximately $7.2 million increase in external expenses. Included in the increase are an approximately $5.3 million increase in consulting and professional expenses for our pre-commercialization efforts and an approximately $1.9 million increase in other professional fees and expenses, which consist primarily of legal, auditing, consulting and investor relations fees; and
- an approximately $5.3 million increase in internal expenses. Included in the increase are an approximately $2.8 million increase in payroll and related costs as administrative headcount increased from 18 to 27, mostly in support of the expected commercial product launch in 2017, an approximately $2.1 million increase in facility and equipment costs and an approximately $0.5 million increase in other expenses primarily attributable to supporting our corporate growth.

Research and development expenses:

Research and development expenses (in thousands)	2017	2016	2015	Annual Percentage Change 2017/2016	2016/2015
External	$89,212	$95,010	$99,184	(6.1 %)	(4.2 %)
Internal	41,057	37,147	31,520	10.5 %	17.9 %
Employee stock-based compensation	77,541	90,641	77,768	(14.5%)	16.6 %
	$207,810	$222,798	$208,472	(6.7 %)	6.9 %

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

For the year ended December 31, 2017, R&D expenses decreased approximately $15.0 million compared to the same period in 2016. The decrease was primarily attributable to:

- an approximately $5.8 million decrease in external expenses. Included in the decrease is an approximately $6.8 million decrease in manufacturing costs related to launch preparation, offset by an approximate $1.0 million increase in clinical study related expenses;
- an approximately $3.9 million increase in internal expenses. Included in the increase is an approximately $3.2 million increase from adding 19 new employees in clinical development and medical affairs and an approximately $0.7 million increase for additional expenses such as travel and software; and
- an approximately $13.1 million decrease in stock-based compensation expense.

We expect R&D expenses in 2018 to continue to decline slightly when compared with R&D expenses in 2017 based on a decline in clinical trial activities as trials begin to wind down.

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 $4.1 million decrease in external expenses primarily from an approximately $14.3 million decrease in CRO expenses partially offset by an approximate increase of $10.2 million in clinical and pre-clinical service expenses, and consultant expense to support the filing of an NDA with the FDA and MAA with the EMA; and
- an approximately $5.6 million increase in internal expenses driven primarily by headcount increases in clinical development, regulatory affairs and manufacturing.

While expenditures on current and future clinical development programs, particularly our PB272 program, are expected to be substantial, they 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.

Other income and expenses:

Other (expenses) income:				Annual Percentage Change			
(in thousands)	2017	2016	2015	2017/2016		2016/2015	
Interest income	$1,256	$958	$971	31.1	%	(1.3	%)
Interest expense	(720)	—	—	—		—	
Other (expenses) income	(101)	(373)	25	(72.9	%)	(1,592.0	%)
Total other (expenses) income	$435	$585	$996	(25.6	%)	(41.3	%)

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

Interest income:

For the year ended December 31, 2017, we recognized approximately $1.3 million in interest income compared to approximately $1.0 million of interest income for the year ended December 31, 2016. The increase in interest income reflects more cash invested in money market accounts and “high yield” savings accounts for 2017 compared to 2016 (see Note 6 in the accompanying notes to consolidated financial statements).

Interest expense:

For the year ended December 31, 2017, we recognized approximately $0.7 million in interest expense compared to $0 of interest expense for the year ended December 31, 2016. This increase in interest expense is as a result of the debt financing which closed in October 2017 (see Note 7 in the accompanying notes to consolidated financial statements).

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

Interest income:

For the year ended December 31, 2016, we recognized approximately $1.0 million in interest income compared to approximately $1.0 million of interest income for the years ended December 31, 2015.

Interest expense:

For the years ended December 31, 2016 and 2015, we did not recognize interest expense as we did not have any debt financing.

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 stock-based compensation. For the three and twelve months ended December 31, 2017, stock-based compensation represented approximately 39.8% and 37.2% 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 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 Adjusted Net Loss and GAAP Net Loss Per Share to Non-GAAP Adjusted Net Loss Per Share

(in thousands except share and per share data)

	For the Year Ended December 31,			
	2017	2016	2015	
GAAP net loss	$(291,955)	$(276,011)	$(239,284)	
Adjustments:				
Stock-based compensation -				
Selling, general and administrative	31,194	26,623	17,166	(1)
Research and development	77,541	90,641	77,768	(2)
Non-GAAP adjusted net loss	$(183,220)	$(158,747)	$(144,350)	
GAAP net loss per share—basic and diluted	$(7.85)	$(8.29)	$(7.45)	
Adjustment to net loss (as detailed above)	2.92	3.52	2.96	
Non-GAAP adjusted net loss per share	$(4.93)	$(4.77)	$(4.49)	(3)

(1) To reflect a non-cash charge to operating expense for selling, 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 37,169,678, 33,295,114 and 32,126,094 weighted average common shares outstanding for the years ended December 31, 2017, 2016 and 2015, respectively.

Liquidity and Capital Resources

Operating Activities

We reported net losses of approximately $292.0 million, $276.0 million and $239.3 million for the years ended December 31, 2017, 2016 and 2015, respectively. We also reported negative cash flows from operating activities of approximately $172.5 million, $141.7 million and $154.5 million for the years ended December 31, 2017, 2016 and 2015, respectively.

Net cash used in operating activities for the year ended December 31, 2017, includes a net loss of $292.0 million adjusted for non-cash items of approximately $108.7 million for stock-based compensation expense, and depreciation of property and equipment and license amortization of approximately $2.8 million. Further changes in cash flows from operations include an increase in accounts payable and accrued expenses of approximately $21.6 million, an increase in accounts receivable of approximately $9.7 million, an increase in inventory of approximately $2.0 million, an increase in prepaid expenses and other of approximately $1.1 million and an decrease in the accrued liability for deferred rent of approximately $0.1 million.

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.

Investing Activities

Net cash used in investing activities was approximately $15.4 million for the year ended December 31, 2017. This includes an increase in intangible assets of approximately $50.0 million, the purchase of available-for-sale securities of approximately $79.7 million, offset by the maturity of available-for-sale securities of approximately $114.7 million and cash used for the purchase of property and equipment of approximately $0.4 million as provided the newly hired salesforce with computer and phone equipment for commercial launch of NERLYNX.

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.

Financing Activities

October 2017 Debt Financing

On October 31, 2017, we entered into a loan agreement for a term loan of up to $100.0 million, subject to funding in two tranches. We received proceeds net of fee associated with the initiation and interest fees of $48.5 million from the first tranche of the credit facility upon closing on October 31, 2017 and intend to use the funds for general corporate purposes and to further support NERLYNX commercial initiatives. The second tranche of $50.0 million less associated fees per the financing agreement may be drawn at our option between March 31, 2018 and June 30, 2018 provided we have achieved a specified minimum revenue milestone and no event of default is occurring. The loan will mature on October 31, 2022.

Other Financing Activities

In addition, during the year ended December 31, 2017, approximately $26.7 million was received for employee stock options exercised during 2017.

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 offering expenses.

Other Financing Activities

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 underwriting discounts and commissions. The net proceeds received by us were approximately $205.1 million after deducting underwriting discounts and commissions and offering expenses.

Other Financing Activities

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

Loan and Security Agreement

On October 31, 2017, or the Effective Date, we entered into a loan and security agreement, or the credit facility, with Silicon Valley Bank, as administrative and collateral agent, or SVB, and the lenders party thereto from time to time, including Oxford Finance LLC and SVB, pursuant to which the lenders agreed to make term loans available to us in an aggregate amount of $100 million, consisting of (i) an aggregate amount of $50 million available on the Effective Date and (ii) an aggregate amount of $50 million available to be drawn at our option between March 31, 2018 and June 30, 2018, provided we have achieved a specified minimum revenue milestone and no event of default is occurring. Proceeds from the term loans may be used for working capital and general business purposes. The credit facility is secured by substantially all of our personal property other than our intellectual property. We also pledged 65% of the issued and outstanding capital stock of our subsidiary, Puma Biotechnology Ltd. The credit facility limits our ability to grant any interest in our intellectual property to certain permitted licenses and permitted encumbrances set forth in the agreement.

The term loans under the credit facility bear interest at an annual rate equal to the greater of (i) 7.75% and (ii) the sum of (a) the "prime rate," as reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue, plus (b) 3.5%. We are required to make monthly interest-only payments on each outstanding term loan commencing on the first calendar day of the calendar month following the funding date of such term loan, and continuing on the first calendar day of each calendar month thereafter through December 1, 2019. Commencing on December 1, 2019, and continuing on the first calendar day of each calendar month thereafter, we are required to make consecutive equal monthly payments of principal, together with applicable interest, in arrears to each lender, calculated pursuant to the credit facility. All unpaid principal and accrued and unpaid interest with respect to each term loan is due and payable in full on October 31, 2022. Upon repayment of the term loans, we are also required to make a final payment to the lenders equal to 7.5% of the original principal amount of term loans funded.

At our option, we may prepay the outstanding principal balance of any term loan in whole but not in part, subject to a prepayment fee of 2.0% of any amount prepaid if the prepayment occurs through and including the first anniversary of the funding date of such term loan, or 1.0% of the amount prepaid if the prepayment occurs after the first anniversary of the funding date of such term loan through and including the second anniversary of the funding date of such term loan.

The credit facility includes affirmative and negative covenants applicable to us, our current subsidiary and any subsidiaries we may create in the future. The affirmative covenants include, among others, covenants requiring us to maintain our legal corporate existence and governmental approvals, deliver certain financial reports, maintain insurance coverage and satisfy certain requirements regarding deposit accounts. We must also achieve product revenue, measured as of the last day of each fiscal quarter on a trailing three-month basis, that is (i) greater than or equal to 70% of our revenue target set forth in our board-approved projections for the 2017 fiscal year, (ii) greater than or equal to 50% of our revenue target set forth in our board-approved projections for the 2018 fiscal year, and (iii) greater than or equal to 50% of our revenue target set forth in our board-approved projections for the 2019 fiscal year. New minimum revenue levels will be established for each subsequent fiscal year by our mutual agreement with SVB, as administrative agent, and the lenders. The negative covenants include, among others, restrictions on us transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, making investments, creating liens, selling assets and suffering a change in control, in each

case subject to certain exceptions.

The credit facility also includes events of default, the occurrence and continuation of which could cause interest to be charged at the rate that is otherwise applicable plus 5.0% and would provide SVB, as collateral agent, with the right to exercise remedies against us and the collateral securing the credit facility, including foreclosure against the property securing the credit facilities, including its cash. These events of default include, among other things, any failure by us to pay principal or interest due under the credit facility, a breach of certain covenants under the credit facility, our insolvency, a material adverse change, the occurrence of any default under certain other indebtedness in an amount greater than $500,000 and one or more judgments against us in an amount greater than $500,000 individually or in the aggregate.

Current and Future Financing Needs

We have incurred negative cash flows from operations since we started our business, and we did not achieve any product revenues until the third quarter of 2017. 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 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 $130 million to $140 million, excluding stock-based compensation.

Additionally, we expect SG&A expenses to increase as we continue 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 totaling approximately $81.7 million available at December 31, 2017. 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. 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.

In addition, we have based our estimate of 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. Although we may have access to the additional $50 million from the debt financing during 2018 provided we have achieved a specified minimum revnue milestone and no event of default is occurring, 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, 2017 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. We also have unrecognized tax benefits that, if recognized, would affect the effective tax rate at December 31, 2017. We do 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. 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, 2017, 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	$43,862	$4,472	$10,000	$10,764	$18,626
Debt (principal and interest)	67,345	3,929	43,789	19,627	—
Total	$111,207	$8,401	$53,789	$30,391	$18,626

See Note 10—Taxes and Note 11—Commitments and Contingencies in the accompanying notes to the financial statements for a summary of the Company's uncertain tax positions and contracts held by the Company as of December 31, 2017.

Critical Accounting Policies

The 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 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.

Revenue Recognition:

We adopted Accounting Standards Codification ("ASC") Topic 606 - Revenue from Contracts with Customers ("Topic 606") on January 1, 2017. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements, and financial instruments. Under Topic 606, an entity recognizes revenue when its customer obtains control of the promised goods or services, in an amount that reflects the consideration which the entity expects to be entitled in exchange for those goods or services. We had no contracts with customers until the FDA approved NERLYNX on July 17, 2017. Subsequent to receiving FDA approval, we entered into a limited number of arrangements with specialty pharmacies ("SPs") and specialty distributors ("SDs") in the United States, which we refer to as our Customers, to distribute NERLYNX. These arrangements are our initial contracts with customers. We have determined that these sales channels with customers are similar.

Reserves for Variable Consideration:

Revenue from product sales are recorded at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established. Components of variable consideration include trade discounts and allowances, product returns, provider chargebacks and discounts, government rebates, payor rebates, and other incentives, such as voluntary patient assistance, and other allowances that are offered within contracts between us and our Customers, payors, and other indirect customers relating to the sale of our products. These reserves, as detailed below, are based on the amounts earned, or to be claimed on the related sales, and are classified as reductions of accounts receivable or a current liability. These estimates take into consideration a range of possible outcomes which are probability-weighted in accordance with the expected value method in Topic 606 for relevant factors such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which it is entitled based on the terms of the respective underlying contracts.

The amount of variable consideration which is included in the transaction price may be constrained, and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative

revenue recognized under the contract will not occur in a future period. Our analyses also contemplated application of the constraint in accordance with the guidance, under which it determined a material reversal of revenue would not occur in a future period for the estimates detailed below as of December 31, 2017 and, therefore, the transaction price was not reduced further during the year ended December 31, 2017. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Trade Discounts and Allowances:

We generally provide Customers with discounts which include incentive fees that are explicitly stated in our contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we compensate (through trade discounts and allowances) our Customers for sales order management, data, and distribution services. However, we have determined

such services received to date are not distinct from our sale of products to the Customer and, therefore, these payments have been recorded as a reduction of revenue within the statement of operations and comprehensive loss through December 31, 2017.

Product Returns:

Consistent with industry practice, we offer the SPs and SDs limited product return rights for damaged and expiring products, provided it is within a specified period around the product expiration date as set forth in the applicable individual distribution agreement. We estimate the amount of our product sales that may be returned by our Customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized, as well a reduction to trade receivables, net on the consolidated balance sheets. We currently estimate product returns using available industry data and our sales information, including our visibility into the inventory remaining in the distribution channel. We have an insignificant amount of returns to date and believe that returns of our products will continue to be minimal.

Provider Chargebacks and Discounts:

Chargebacks for fees and discounts to providers represent the estimated obligations resulting from contractual commitments to sell products to qualified healthcare providers at prices lower than the list prices charged to Customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability. Chargeback amounts are generally determined at the time of resale to the qualified healthcare provider by Customers, and we generally issue payments for such amounts within a few weeks of the Customer’s notification to us of the resale. Reserves for chargebacks consist of payments that we expect to issue for units that remain in the distribution channel at each reporting period-end that we expect will be sold to qualified healthcare providers, and chargebacks that Customers have claimed, but for which we have not yet issued a payment.

Government Rebates:

We are subject to discount obligations under state Medicaid programs and Medicare. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included in accrued expenses and other current liabilities on the consolidated balance sheets. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. Our liability for these rebates consists of invoices received for claims from prior quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimated future claims that will be made for product that has been recognized as revenue, but which remains in the distribution channel at the end of each reporting period.

Payor Rebates:

We contract with certain private payor organizations, primarily insurance companies and pharmacy benefit managers, for the payment of rebates with respect to utilization of its products. We estimate these rebates and records such estimates in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability.

Other Incentives:

Other incentives which we offer include voluntary patient assistance programs, such as the co-pay assistance program, which are intended to provide financial assistance to qualified commercially-insured patients with prescription drug co-payments required by payors. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue, but remains in the distribution channel at the end of each reporting period. The adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included as a component of accrued expenses and other current liabilities on the consolidated balance sheets.

Recently Issued Accounting Standards

In May 2014, the Financial Accounting Standards Board, FASB, issued a new accounting standard that amends the guidance for the recognition of revenue from contracts with customers to transfer goods and services. The FASB has subsequently issued additional, clarifying standards to address issues arising from implementation of the new revenue recognition standard. The new revenue recognition standard and clarifying standards are effective for interim and annual periods beginning on January 1, 2018, but could have been adopted early beginning January 1, 2017. We chose to adopt this standard in 2017 as we began to first generate revenue, with no revenue

recognized in prior years. We have also identified and implemented changes to our accounting policies, business processes, and internal controls to support the new accounting and disclosure requirements.

In January 2016, the FASB issued ASU No. 2016-01, Recognition and Measurement of Financial Assets and Financial Liabilities. ASU No. 2016-01 requires equity investments to be measured at fair value with changes in fair value recognized in net income; simplifies the impairment assessment of equity investments without readily determinable fair values by requiring a qualitative assessment to identify impairment; eliminates the requirement for public business entities to disclose the method(s) and significant assumptions used to estimate the fair value that is required to be disclosed for financial instruments measured at amortized cost on the balance sheet; requires public business entities to use the exit price notion when measuring the fair value of financial instruments for disclosure purposes; requires an entity to present separately in other comprehensive income the portion of the total change in the fair value of a liability resulting from a change in the instrument-specific credit risk when the entity has elected to measure the liability at fair value in accordance with the fair value option for financial instruments; requires separate presentation of financial assets and financial liabilities by measurement category and form of financial assets on the balance sheet or the accompanying notes to the condensed consolidated financial statements and clarifies that an entity should evaluate the need for a valuation allowance on a deferred tax asset related to available-for-sale securities in combination with the entity's other deferred tax assets. ASU No. 2016-01 is effective for financial statements issued for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. We are currently evaluating the impact that ASU No. 2016-01 will have on our consolidated financial statements and related disclosures.

In February 2016, the FASB issued Accounting Standards Update, or 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 their balance sheet the assets and liabilities for the rights and obligations created by those leases. Consistent with current 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 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. We are currently in the process of evaluating the impact of ASU 2016-02 on our outstanding leases and expects that adoption will have an impact on the consolidated balance sheets related to recording right-of-use assets and corresponding lease liabilities.

In March 2016, the FASB issued ASU No. 2016-09, Compensation – Stock Compensation: Improvements to Employee Share-Based Payment Accounting, which was intended to simplify various aspects of accounting for share-based payment transactions. The new guidance requires immediate recognition of all excess tax benefits and deficiencies in the income statement; requires classification of excess tax benefits as an operating activity as opposed to a financing activity in the statements of cash flows; requires the classification of cash paid by an employer when directly withholding shares for tax-withholding purposes be classified as a financing activity on the statements of cash flows; and allows us to make an accounting policy election to either estimate the number of awards expected to vest or account for forfeitures when they occur. The standard is effective for annual reporting periods beginning after December 15, 2016, and interim periods within those annual reporting periods. We applied an accounting policy election to estimate forfeitures and then true up actual forfeitures as they occur. Because this treatment was in line with our current treatment of forfeitures, the impact was insignificant as of December 31, 2017. This adoption resulted in a one-time net increase to the net operating losses deferred tax asset and the corresponding valuation allowance of $184.1 million at the federal and state level, which is a primarily cumulative adjustment for the

previously unrecognized windfall tax benefits related to previous vesting and exercises of stock-based awards. We applied this standard in the first quarter of 2017 using the modified retrospective transition method of adoption. Due to the full valuation allowance on the deferred tax assets, the adoption did not have any impact on our consolidated financial statements on the adoption date. In addition, under the new standard, we will prospectively reflect the tax deficiencies and benefits as an operating activity, rather than as a financing activity under the previous standard, in our Consolidated Statements of Cash Flows.

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. We are currently evaluating the impact of adopting ASU 2016-15 on our 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 us in the fiscal year beginning after December 15, 2017, but early adoption is permissible. We are currently evaluating the effect that the adoption of ASU 2016-18 will have on our consolidated financial statements.

In July 2015, the FASB issued ASU 2015-11, Inventory (Topic 330): Simplifying the Measurement of Inventory, which requires an entity to measure inventory at the lower of cost and net realizable value, and eliminates current GAAP options for measuring market value. ASU 2015-11 defines realizable value as the estimated selling prices in the ordinary course of business, less reasonably predictable costs of completion, disposal, and transportation. ASU 2015-11 was adopted by the Company in fiscal year 2017, and interim periods therein without a material impact to the financial statements. We measure our inventory at the lower of cost and net realizable value.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Some of the securities that we invest in have market risk in that a change in prevailing interest rates may cause the principal amount of the cash equivalents to fluctuate. Financial instruments that potentially subject us to significant concentrations of credit risk consist primarily of cash and cash equivalents. We invest our excess cash primarily in cash equivalents such as money market investments as of December 31, 2017. The primary objectives of our investment activities are to ensure liquidity and to preserve principal while at the same time maximizing the income we receive from our cash and cash equivalents without significantly increasing risk. Additionally, we established guidelines regarding approved investments and maturities of investments, which are designed to maintain safety and liquidity.

Because of the short-term maturities of our cash equivalents, we do not believe that a 10% increase in interest rates would have a material effect on the realized value of our cash equivalents.

We also have interest rate exposure as a result of our outstanding $100.0 million secured term loan from SVB and Oxford. As of December 31, 2017, the outstanding principal amount of the term loan was $50.0 million. The term bears interest at an annual rate equal to the greater of (i) 7.75% and (ii) the sum of (a) the “prime rate,” as reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue, plus (b) 3.5%. Changes in the prime rate may therefore affect our interest expense associated with the term loan.

We do not believe that a 10% increase in the prime rate on December 31, 2017 would have had a material effect on our interest expense as of that date.

ITEM 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.

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

Not applicable.

ITEM 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, 2017. 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, 2017.

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, 2017, that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting, other than controls that were a result of the loan and security agreement entered into on October 31, 2017.

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, 2017. 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, our management concluded that, as of December 31, 2017, our internal control over financial reporting was effective.

Our internal control over financial reporting as of December 31, 2017 has been audited by KPMG LLP, our independent registered public accounting firm, as stated in their report, which expresses an unqualified opinion on the effectiveness of our internal control over financial reporting as of December 31, 2017.

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors

Puma Biotechnology, Inc.:

Opinion on Internal Control Over Financial Reporting

We have audited Puma Biotechnology, Inc. and subsidiary (the Company) internal control over financial reporting as of December 31, 2017, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2017, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheet of the Company as of December 31, 2017, and the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for the year ended December 31, 2017,and the related notes (collectively, the consolidated financial statements), and our report dated March 9, 2018 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible 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 the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. 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 audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

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 generally accepted accounting principles. 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 generally accepted accounting principles, 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 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.

/s/ KPMG LLP

Los Angeles, California

March 9, 2018

ITEM 9B. OTHER INFORMATION

On December 15, 2017, the compensation committee of our board of directors approved the ratification, or the Ratification, of certain grants of Restricted Stock Units, or the RSU Awards, under the Puma Biotechnology, Inc. 2011 Incentive Award Plan, as amended, pursuant to and in accordance with Section 204 of the General Corporation Law of the State of Delaware, or the General Corporation Law. The RSU Awards were made on August 28, 2017, September 11, 2017, September 18, 2017, September 25, 2017 and October 2, 2017 and involved the grant of 43,500, 18,750, 2,000, 7,500 and 13,125 Restricted Stock Units, respectively. The compensation committee approved the Ratification of such RSU Awards after it determined that the RSU Awards may not have been duly authorized in accordance with Section 152 of the General Corporation Law. As none of the RSU Awards have vested, no shares of putative stock have been issued in respect of the RSU Awards. Any claim that the RSU Awards are void or voidable due to the foregoing failure of authorization, or that the Court of Chancery of the State of Delaware should declare in its discretion that the Ratification not be effective or be effective only on certain conditions, must be brought within 120 days from the later of the validation effective time and the giving of this notice (which is deemed given on the date that this Annual Report on Form 10-K is filed with the Securities and Exchange Commission).

Part III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item will be included in our 2018 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item will be included in our 2018 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

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

The information required by this Item will be included in our 2018 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item will be included in our 2018 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by this Item will be included in our 2018 Proxy Statement, which will be filed with the SEC, and is incorporated by reference herein.

Part IV

ITEM 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.

ITEM 16. Form 10-K SUMMARY

None.

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	8-K	3.2	10/11/2011

	Corp., filed with the Secretary of State of the State of Delaware on October 4, 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	Second Amended and Restated Bylaws of Puma Biotechnology, Inc.	8-K	3.1	5/8/2017
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,	10-Q	10.1	11/10/2014

	between the Company and Pfizer, Inc.			
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)#	Third Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan	8-K	10.1	6/14/2017
10.2(e)#	Fourth Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan	8-K	10.2	6/14/2017
10.2(f)#	Puma Biotechnology, Inc. 2017 Employment Inducement Incentive Award Plan			