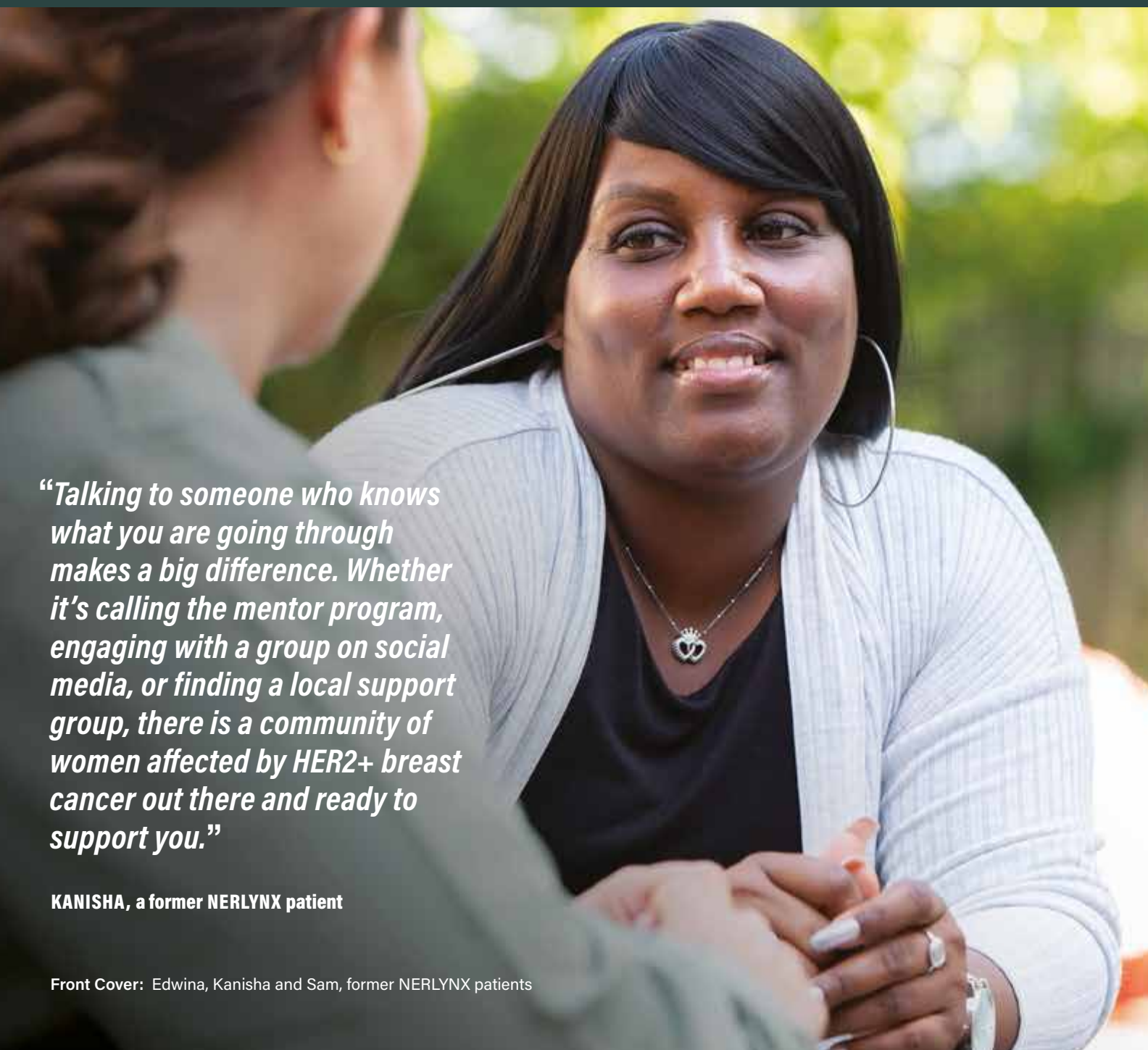
# THE FACES OF BREAST CANCER

**PUMA BIOTECHNOLOGY, INC.** | 2021 ANNUAL REPORT

Puma's lead drug NERLYNX® was approved by the U.S. Food and Drug Administration in 2017 for the extended adjuvant treatment of early stage HER2-positive breast cancer and in 2020 as combination therapy for the treatment of advanced or metastatic HER2-positive breast cancer following two or more prior HER2-based regimens in the metastatic setting. Thousands of breast cancer patients have since been treated with NERLYNX. We will highlight some of those patients throughout this report.



***"Talking to someone who knows what you are going through makes a big difference. Whether it's calling the mentor program, engaging with a group on social media, or finding a local support group, there is a community of women affected by HER2+ breast cancer out there and ready to support you."***

**KANISHA, a former NERLYNX patient**

**Front Cover:** Edwina, Kanisha and Sam, former NERLYNX patients

**PUMA BIOTECHNOLOGY, INC.** is a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. Puma in-licenses the global development and commercialization rights to PB272 (neratinib, oral), PB272 (neratinib, intravenous), and PB357.

Neratinib is a potent irreversible tyrosine kinase inhibitor that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Puma has been focused on developing the oral version of neratinib, and its most advanced drug candidates are directed at the treatment of HER2-positive breast cancer. Puma believes that neratinib has clinical applications in the treatment of several other cancers as well, including non-small cell lung cancer and other solid tumor types that over-express or have a mutation in HER2.

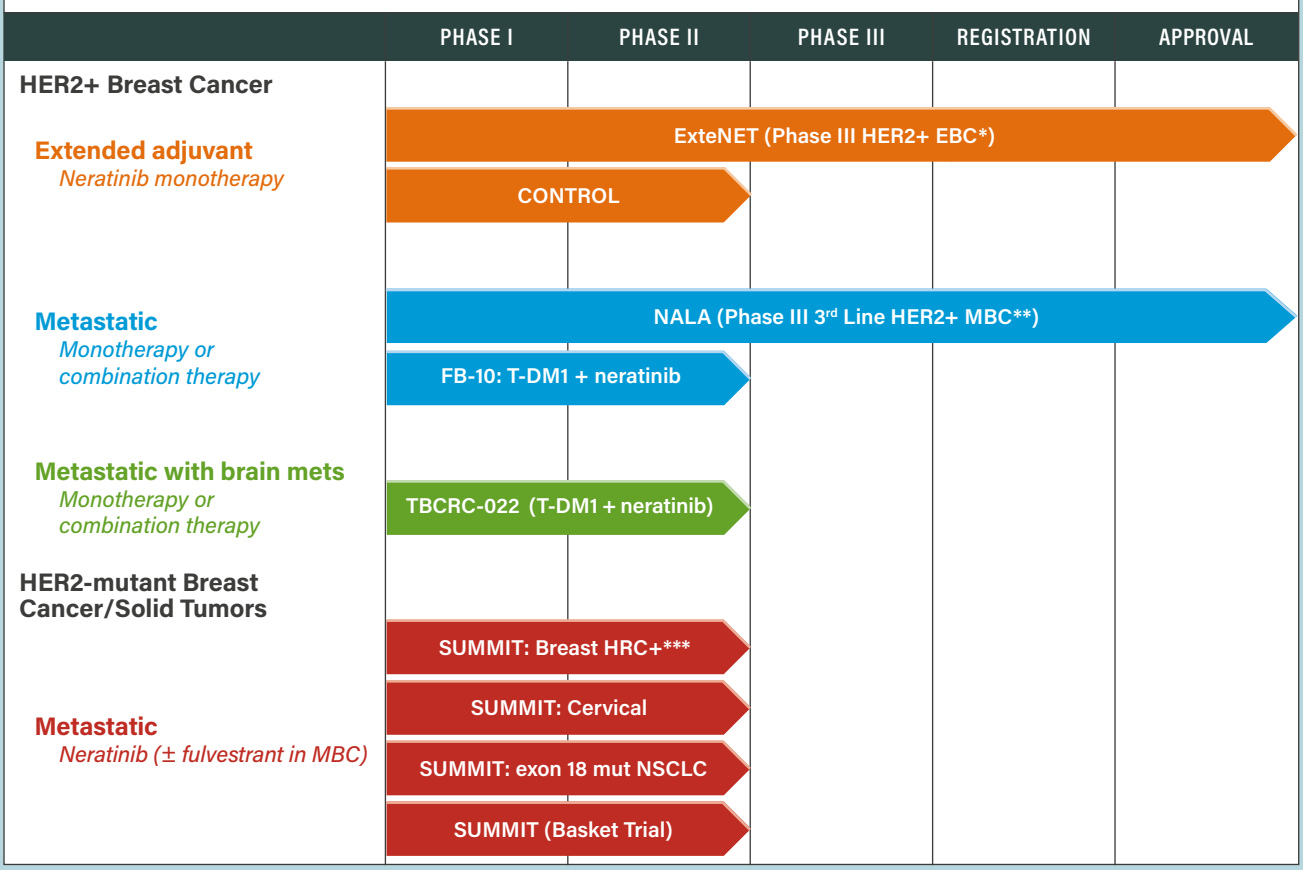
Neratinib, oral was approved by the U.S. Food and Drug Administration in 2017 for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, following adjuvant trastuzumab-based therapy. Puma commenced commercial sales of the drug in 2017 and it is marketed in the United States as NERLYNX® tablets. In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. NERLYNX was granted marketing authorization by the European Commission in 2018 for the extended adjuvant treatment of adult patients with early stage hormone receptor-positive HER2-overexpressed/amplified breast cancer and who are less than one year from completion of prior adjuvant trastuzumab-based therapy. Commercial sales commenced in the European Union in 2019.

Puma has entered into additional exclusive license agreements with various parties to commercialize NERLYNX in regions outside the United States, including the European Union, Canada, Latin America, Greater China, Israel, Southeast Asia, Australia, New Zealand, South Korea, the Middle East, and parts of Africa. Puma plans to continue to pursue the commercialization of NERLYNX outside the United States.

NERLYNX® is a registered trademark of Puma Biotechnology, Inc.

## PRODUCT PIPELINE

*Neratinib across the breast cancer therapy spectrum*




* **EBC:** Early breast cancer ** **MBC:** Metastatic breast cancer *** **HRC+:** Hormone receptor positive

# TO OUR STOCKHOLDERS

Puma Biotechnology is committed to developing drugs to help cancer patients. In 2017, the U.S. Food and Drug Administration (FDA) approved neratinib (marketed as NERLYNX®) for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy. In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

In a patient's fight against early stage breast cancer, patients are faced with risk of the recurrence of disease. Puma is taking a stance against the recurrence of breast cancer; our greatest inspiration has been our patients, the faces of NERLYNX®. Our patients are their own greatest advocates, and Puma stands with them and for them in this fight against recurrence. These patients are waging battles against cancer and trying to win. After this arduous journey, the worst news a survivor can receive is learning their cancer has returned. We are motivated to ensure that *life continues* for those in this fight. Our goal is to introduce our therapy to every mother, partner, friend, sister and aunt, as well as all of the male patients who may benefit from it. We are proud to have some of our patients highlighted throughout this report.

## LOOKING TO THE FUTURE: EMPOWERMENT AND ENGAGEMENT

While disease progression management is clinically addressed through NERLYNX therapy, Puma empowers and supports patients in all dimensions of their wellbeing, helping them understand the prognosis and come to terms with challenges, allowing for the planning and preparation of all aspects of their journey. We know that people resonate with and learn from others' experiences. Puma provides a platform for patients to share their stories and we want to empower these individuals to help support others. We encourage our patients to be vocal about life beyond their breast cancer diagnosis.

We have launched a mentoring program through which cancer survivors are paired with newly diagnosed patients. Our goal is to help both parties cope, understand, and adapt. The journey with cancer is exceptionally hard, and we hope to empower our patients, both physically and emotionally. Our patient advocates and mentors know about these challenges firsthand. They help patients understand the risks, benefits, side effects, and general impact of treatment with NERLYNX. Through these advocates, we have been able to communicate important information about HER2-positive breast cancer with our communities and educate them about the risks and benefits of our drug.

We want our patients to continue their lives as normally as possible and we are willing to go to great lengths to make this happen. Our goal is to enable a recovering mother to play with her children, a young entrepreneur to expand her business, a teacher to guide her students, and all others affected to keep thriving. There is life after cancer, and our goal is to prevent recurrence.

## IMPROVING AND INNOVATING TO CREATE A BETTER TREATMENT PROFILE FOR NERATINIB

Expanding the range of cancers that neratinib can successfully treat requires dedicated clinical focus, which we are addressing through our clinical trials and clinical collaborations. The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of leading cancer centers devoted to patient care, research, and education, announced that they will focus on three projects to evaluate neratinib in various tumor types, in partnership with Puma. We are excited to support this initiative that brings us closer to our mission of exploring the efficacy of neratinib in a diverse range of cancers.

- **CONTROL Phase II Trial**

The CONTROL Phase II study is a multicenter, multi-cohort, open-label study investigating methods to improve the tolerability of neratinib in patients with early stage, HER2-positive breast cancer. Participating patients were evaluated based on their response to neratinib with loperamide prophylaxis plus additional anti-diarrheal treatments and to gradual dose escalation of

**Alan H. Auerbach**
*Chairman, Chief Executive Officer, President and Founder*

neratinib with loperamide as needed. The latter demonstrated an 80% reduction in rates of discontinuation due to diarrhea when compared to an ExteNET trial cohort where dose escalation or antidiarrheals were not mandated. Results comparing the findings from Puma's CONTROL and ExteNET studies were presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting and confirmed that neratinib dose-escalation lowers the frequency of severe diarrhea and improves its overall tolerability in HER2-positive early stage breast cancer patients.

NERLYNX received approval for a Dose Escalation Label Update from the FDA validating the findings from the CONTROL trial that showed improved management and prevention of Grade 3 diarrhea is possible through gradual dose titration.

- **SUMMIT Phase II Trial**

Puma's Phase II SUMMIT Trial is investigating the efficacy and safety of neratinib in patients with (i) HER2 mutant metastatic salivary gland cancer; (ii) EGFR exon 18 mutation-positive lung cancer; (iii) HER2 mutant cervical cancer; (iv) HER2 mutant solid tumors; (v) HER2 mutant bladder cancer; (vi) HER2 mutant HRc positive breast cancer; (vii) HRc negative breast cancer; and (viii) HER4 mutant solid tumors.

An interim update from the cohort of metastatic non-small cell lung cancer (NSCLC) patients with EGFR exon 18 mutations, previously treated with an EGFR targeted tyrosine kinase inhibitor (TKI) from the SUMMIT trial was presented at the 2020 World Conference on Lung Cancer (WCLC 2020) in January 2021. Efficacy results showed that for the 10 evaluable patients who were previously treated with TKI, 6 patients (60%) experienced a partial response, including 4 patients (40%) with confirmed partial response, and 8 patients (80%) experienced clinical benefit, which is a confirmed complete response or partial response or stable disease for at least 16 weeks. At the 2021 ASCO Annual Meeting, another update was presented from a subgroup of the above cohort. 11 patients with EGFR exon 18-mutant NSCLC, including patients with central nervous system involvement, were evaluated for safety and efficacy. Study results from this subgroup of patients showed that neratinib is a potentially efficacious and safe treatment option for patients with EGFR exon 18-mutant lung cancer for whom targeted treatment options do not exist. Both of these findings are critical as they offer a potential alternative to patients for whom few effective treatment options are available after they fail first-line FDA-approved EGFR TKI therapy.

At the 2021 Gastrointestinal Cancers Symposium presented by the American Society of Clinical Oncology (ASCO GI), we shared findings from the cohort evaluating the safety and efficacy of neratinib administered daily to patients who have HER2 (ERBB2) mutation-positive advanced biliary cancer. It was shown that neratinib was safe and tolerable in these patients and had comparable activity to current standard treatments, leading to similar progression-free survival and overall survival.

Puma delivered an oral presentation, and presented additional posters, at the 2021 San Antonio Breast Cancer Symposium (SABCS) Annual Meeting late last year showcasing updates from the SUMMIT Phase II Trial. The findings indicated that combination therapy with neratinib, fulvestrant, and trastuzumab is a promising new treatment option for patients with hormone receptor-positive, HER2-mutant metastatic breast cancer (MBC) exposed to CDK4/6 inhibitors and a separate cohort of patients with metastatic triple-negative breast cancer (TNBC) with a HER2 mutation.

- **ExteNET Phase III Trial**

At the Virtual 2021 ASCO Annual Meeting, Puma presented results from the ExteNET trial that showed improved outcomes in all evaluated endpoints in patients with HER2-positive early stage breast cancer who could tolerate neratinib treatment for 11 months or more. The findings indicated that overall survival in patients is improved upon completion of neratinib extended adjuvant therapy and could be beneficial in patients with early stage HER2-positive breast cancer who are at a high risk of relapse.

ExteNET was a multicenter, randomized, double-blind, Phase III trial of 2,840 HER2-positive early stage breast cancer patients who received NERLYNX after neoadjuvant and/or adjuvant therapy with chemotherapy and trastuzumab. Patients were stratified by hormone receptor status and randomly assigned to one year of treatment with either oral neratinib 240 mg/day or placebo.

## FINANCIALS

In late 2021, Puma adopted several important organizational changes within the company that had two major goals—synergize workflows and simplify the reporting structure to better deploy financial resources for maximum efficiency by adapting to the ever-developing oncology market.

The ongoing COVID-19 pandemic has presented challenges to our commercial operations, primarily in sales and logistics, but Puma quickly adapted and successfully delivered on our clinical goals. The long-term health of our patients remains our priority, a focus that is unwavering in all we do.

For the full year 2021, Puma reported a net loss of $29.1 million, or $0.72 per share, compared to a net loss of $60.0 million, or $1.52 per share, in 2020. Net product revenue from NERLYNX was $189.1 million. We completed the year with $82.1 million in cash, cash equivalents, and marketable securities.

In November of 2021, the United States Patent and Trademark Office (USPTO) issued a Patent Term Extension Certificate for Puma's U.S. Patent No. 7,399,865, extending the term for NERLYNX (neratinib) five years to 2030. Despite the financial turbulence that has plagued the biopharmaceutical sector in the past year, this provides us with an opportunity to invest in the drug and look at potential ways NERLYNX can help treat cancer patients.

## LOOKING AHEAD TO 2022 AND BEYOND

Puma remains focused on leveraging the positive clinical data for NERLYNX—engaging, and informing patients about NERLYNX and empowering them to voice their concerns—and amplifying our impact through strategic outreach across the globe.

There is a significant unmet need to help breast cancer patients prevent recurrence. We are committed and passionate about finding more effective ways at helping these patients during their journey and we will continue to strive to achieve that goal.

As always, Puma could not have achieved its milestones in 2021 without the support of our patients, physicians, employees, and stockholders. On behalf of the company and our Board of Directors, I would like to take this opportunity to sincerely thank all stakeholders for their continued encouragement and support in our mission to provide cancer care.

Sincerely,

**Alan H. Auerbach**

Chairman, Chief Executive Officer, President and Founder


*"NERLYNX sounded like a drug I wanted to take. Most important to me is that it helps to prevent recurrence and it crosses the blood-brain barrier. I will do anything to reduce the chance of recurrence and taking NERLYNX was comforting to me."*
**EDWINA, a former NERLYNX patient**

*"I don't want to have a recurrence. Anything I can do to not have one is what I'm going to do."*

**SAM, a former NERLYNX patient**

*"I felt really strongly about Erin going on NERLYNX and completing one year. The data shows really robust disease prevention and NERLYNX therapy also helps in preventing CNS and brain metastases."*

**JOHN, PA-C/APP, a member of ERIN'S healthcare team**

*"It's important for the medical community to be reminded of the faces behind the data. I am not a percentage. I am a face, not a number. I am a patient advocate, a coach, an outdoor enthusiast, a friend, and a former NERLYNX patient. Choosing NERLYNX enabled me to take a stand against recurrence and gave me great hope...."*

**ERIN, a former NERLYNX patient**

# WE ARE THE FACES OF BREAST CANCER

The women highlighted throughout this report are actual patients who have completed NERLYNX therapy.

**MENTOR PROGRAM**

When you start taking NERLYNX® (neratinib), the mentor program connects you with someone who currently takes or has taken NERLYNX and can share their experience with you. Hearing from someone who has taken NERLYNX helps you:

- Learn about another person's real-life experiences with NERLYNX
- Understand why they felt NERLYNX was right for them
- Learn about the resources available as you take NERLYNX

*https://nerlynx.com/*

# 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 1934exhibit**

**For the fiscal year ended December 31, 2021**

**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 | Trading symbol | Name of each exchange on which registered |
|---|---|---|
| Common Stock, par value $0.0001 per share | PBYI | 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 every Interactive Data File required to be submitted 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 such files). Yes ☒ No ☐

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 | ☐ | 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

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 approximately $373.9 million as of June 30, 2021, based upon the closing price of $9.18 per share of the registrant's common stock on the NASDAQ Global Select Market on Thursday, June 30, 2021, 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 25, 2022, there were 41,332,920 shares of the registrant's common stock outstanding.

Documents Incorporated by Reference:

Portions of the Proxy Statement for the registrant's 2022 Annual Meeting of Stockholders, or the 2022 Proxy Statement, are incorporated by reference into Part III of the Form 10-K to the extent stated herein.

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**TABLE OF CONTENTS**

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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 ("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) tablets ("NERLYNX");
- the development of our drug candidates, including when we expect to undertake, initiate and complete clinical trials of our product candidates;
- the impact of the global COVID-19 pandemic, and measures to control the spread of COVID-19, on business, financial condition, results of operations and ongoing trials;
- the anticipated timing of regulatory filings;
- the regulatory approval of our drug candidates;
- our use of clinical research organizations ("CRO") and other contractors;
- our ability to find collaborative partners for research, development and commercialization of potential products;
- efforts of our sub-licensees to obtain regulatory approval and commercialize NERLYNX in areas outside the United States;
- our ability to market any of our products;
- 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 any litigation to which we are or may become party;
- our ability to in-license additional drugs;
- our ability to attract and retain key personnel; and
- our ability to obtain adequate financing.

These statements are often, but not always, made through the use of words or phrases such as “anticipate,” “estimate,” “plan,” “project,” “continuing,” “ongoing,” “expect,” “believe,” “intend” and similar words or phrases. Accordingly, these statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed in them. Discussions containing these forward-looking statements may be found throughout this Annual Report, including the sections entitled “Item 1. Business” 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, except as required by law. The risks discussed in this Annual Report should be considered in evaluating our prospects and future financial performance.

## SUMMARY OF RISK FACTORS

Our business is subject to a number of risks of which you should be aware before making a decision to invest in our common stock, including those described in the section entitled “Item 1A. Risk Factors” in Part I of this Annual Report. These risks include, among others, the following:

- We have a history of operating losses and are not profitable and may never become profitable.
- We are currently a single product company with limited commercial sales experience.
- We may not be able to successfully commercialize NERLYNX.
- 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.
- The terms of our Note Purchase Agreement 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 Note Purchase Agreement or to satisfy the minimum revenue and cash balance covenants.
- We have limited experience as a company in marketing or distributing pharmaceutical products. If we are unable to expand our marketing and sales capabilities and successfully commercialize NERLYNX, our business, results of operations and financial condition may be materially adversely affected.
- We depend on a limited number of customers for a significant amount of our total revenue, and if we lose any of our significant customers, our business could be harmed.
- Even though the United States Food and Drug Administration ("FDA") and the European Commission ("EC") have granted approval of NERLYNX for the extended adjuvant treatment of early stage, HER2-positive breast cancer and the FDA has granted approval for NERLYNX for the treatment of metastatic HER2-positive breast cancer, the terms of the approvals may limit its commercial potential.
- Interim, “topline” and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.
- NERLYNX or our other drug candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs 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.
- NERLYNX is still under clinical development for various additional indications, and we cannot be certain that NERLYNX will receive regulatory approval for any other indication for which we may seek approval.
- We are dependent on international third-party sub-licensees for the development and commercialization of NERLYNX in several countries outside the United States. The failure of these sub-licensees to meet their contractual, regulatory or other obligations could adversely affect our business.
- We have no experience in drug formulation or manufacturing and 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.
- Our business, financial condition, results of operations and ongoing clinical trials have been and could continue to be harmed by the effects of the COVID-19 pandemic.
- We depend significantly on intellectual property licensed from Pfizer and the termination of this license 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.

**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 together with our wholly-owned subsidiaries, Puma Biotechnology Ltd and Puma Biotechnology B.V.*

We are a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. Our lead product is NERLYNX, an oral version of neratinib, which is a potent irreversible tyrosine kinase inhibitor ("TKI") that blocks signal transduction through the human epidermal growth factor receptors, HER1, HER2 and HER4. In 2017, we obtained approval from the FDA to market, and commenced commercialization of NERLYNX in the United States for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy. More recently, in February 2020, we received FDA approval to expand the indication for NERLYNX to include its use in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. We believe neratinib has clinical application in the treatment of several other cancers as well, including other tumor types that over-express or have a mutation in HER2 or epidermal growth factor receptor ("EGFR") such as cervical cancer, lung cancer or other solid tumors.

Breast cancer is the leading cause of cancer death among women worldwide. Studies show that up to 20% 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, lapatinib (marketed as Tykerb ®) produced by Novartis, fam-trastuzumab deruxtecan (marketed as Enhertu ®) by Astra Zeneca and Daiichi Sankyo and tucatinib (Tukysa ®) marketed by Seagen, 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.

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 breast cancer, including treatment with trastuzumab, pertuzumab, and T-DM1, fam-trastuzumab deruxtecan and tucatinib. We believe that by more potently inhibiting HER2 at a different site and/or acting via a mechanism different from other agents, neratinib may have therapeutic benefits in patients who have been previously treated with these existing treatments, most notably due to its increased selectivity and irreversible inhibition of the HER2 target enzyme.

We currently market NERLYNX in the United States using our direct specialty sales force consisting of approximately 38 sales specialists. Our sales specialists are supported by an experienced sales leadership team consisting of regional managers and directors, as well as a commercial team of experienced professionals in marketing, access and reimbursement, managed markets, marketing research, commercial operations and sales force planning and management. In 2018, the EC granted marketing authorization for NERLYNX in the European Union ("EU") for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. To facilitate our international activities, we have entered into exclusive sub-license agreements with various parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved. We are currently party to several sub-licenses in various regions outside the United States, including Europe (excluding Russia and Ukraine), Australia, Canada, China, Southeast Asia, Israel, South Korea, and various countries and territories in Central America, South America and Africa.

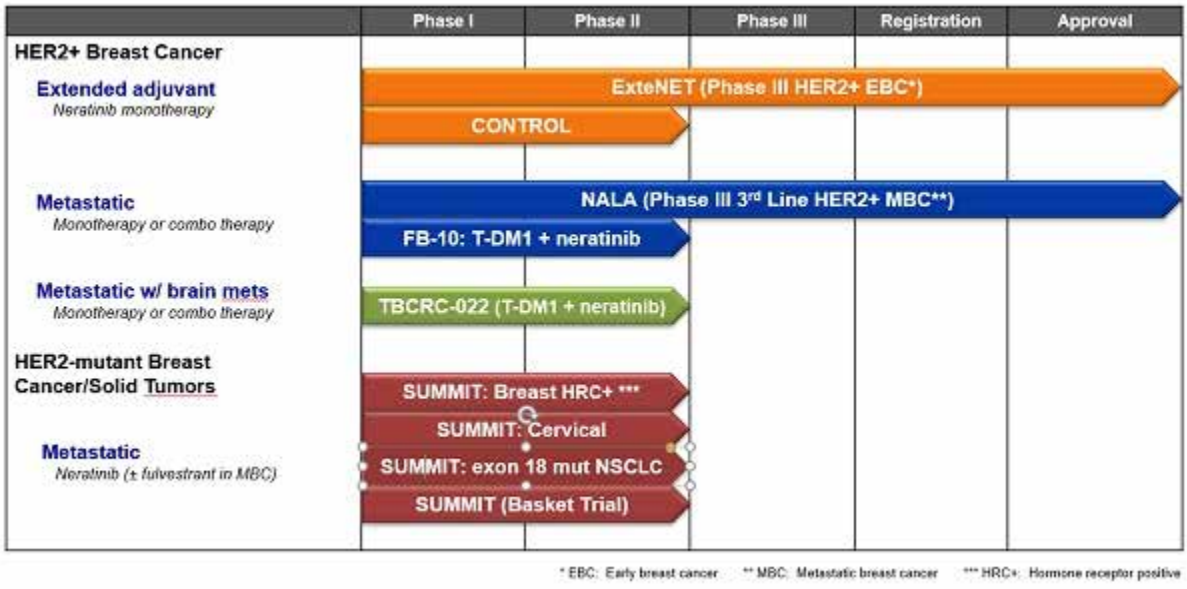
We have also implemented a managed access program for neratinib. Managed access programs provide physicians and patients access to medicines when there are limited or no other therapeutic options available. Our managed access program for neratinib enables participation from countries outside the United States where permitted by applicable rules, procedures and regulatory authorities. The program provides 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 are given neratinib and are instructed to take a prophylaxis which consists of high dose loperamide and budesonide, during treatment to manage neratinib-related diarrhea. We have partnered

with Caligor Opco LLC, which specializes in early access to medicines, to oversee the managed access program for neratinib.

In addition to commercializing NERLYNX for its approved indications, 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 in combination with the drug ado-trastuzumab emtansine (T-DM1, Kadcyla) in patients with HER2-positive metastatic breast cancer that has metastasized to the brain;
- a Phase II clinical trial of neratinib monotherapy or in combination with the drug trastuzumab and/or other anticancer drugs in the treatment of patients with HER2-negative cancers that have a HER2 mutation; and
- a Phase II clinical trial of neratinib monotherapy in patients with non-small cell lung cancer who have an activating EGFR exon 18 mutation.

The following chart shows each of the approved indications of neratinib and those indications currently under development, together with their clinical development stage.




* EBC: Early breast cancer
** MBC: Metastatic breast cancer
*** HRC+: Hormone receptor positive

The following table shows the HER2+ Breast Cancer approvals by disease area and country.

| **Extended adjuvant** | |
|---|---|
| United States | July 2017 |
| European Union | August 2018 |
| Australia | March 2019 |
| Canada | July 2019 |
| Argentina | August 2019 |
| Hong Kong | October 2019 |
| Singapore | November 2019 |
| Switzerland | March 2020 |
| Brunei | April 2020 |
| China | April 2020 |
| Chile | April 2020 |
| New Zealand | June 2020 |
| Taiwan | June 2020 |
| Ecuador | July 2020 |
| Malaysia | July 2020 |
| Peru | March 2021 |
| Macau | August 2021 |
| South Korea | October 2021 |
| Brazil | December 2021 |

| **Metastatic** | |
|---|---|
| United States | February 2020 |
| Argentina | January 2021 |
| Peru | March 2021 |
| Chile | May 2021 |
| Canada | June 2021 |
| Taiwan | October 2021 |

**Strategy**

Our goal is to become a leading provider of advanced therapies for the treatment of various forms of cancer. The following elements comprise our strategy to achieve this objective:

- *Successfully execute our NERLYNX commercial plan.* An important near-term objective is to continue to execute our NERLYNX commercial plan by driving market penetration and duration of therapy consistent with the current NERLYNX label. We continue to focus our efforts on commercializing NERLYNX in the United States. In addition, we have entered into exclusive sub-license agreements with various parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved, in additional countries worldwide.

- *Continue to advance the development of neratinib for the treatment of other HER2-positive, HER2 mutated or EGFR mutated cancer indications.* We are primarily focused on developing neratinib for the treatment of patients with HER2-positive breast cancer, HER2-negative breast cancers with a HER2 mutation and EGFR mutated lung cancer.

- *Expand our product pipeline by pursuing additional applications of neratinib.* We believe there are additional applications for neratinib in the treatment of patients with HER2-negative cancers 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.

- *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 sub-licensees 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 upon or leveraging 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.

- *In-license or acquire additional drug candidates and technologies in order to 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. A decision by us to license a drug candidate will depend on a variety of factors, including 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.

**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. Up to 20% 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 recurrence, 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, T-DM1, fam-trastuzumab deruxtecan and tucatinib 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 treatments for the adjuvant treatment of HER2-positive early stage breast cancer is either the combination of trastuzumab and chemotherapy, the combination of pertuzumab plus trastuzumab and chemotherapy, or Kadcyla, which is approved specifically in patients with HER2-positive early stage breast cancer with residual disease after neoadjuvant treatment. We are aware of a Phase III clinical trial that is comparing trastuzumab plus pertuzumab plus taxane following anthracyclines versus T-DM1 plus pertuzumab following anthracyclines as an adjuvant therapy. In addition, we are also aware of a Phase III trial in patients with high risk HER2-positive early stage breast cancer with residual disease after neoadjuvant treatment that is testing the combination of Kadcyla plus tucatinib versus Kadcyla alone (the CompassHER2 RD Trial) as well as a Phase III trial in patients with high risk HER2-positive early stage breast cancer with residual disease after neoadjuvant treatment that is testing fam-trastuzumab deruxtecan versus Kadcyla alone (the DESTINY-Breast05 Trial).

We believe that there are approximately 30,000 patients in the United States and 37,000 patients in the EU with early stage HER2-positive breast cancer that get treated with adjuvant treatment. We also believe that there are approximately 6,400 patients in the United States with third-line and 4,700 patients in the United States with fourth-line 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.

We believe that approximately 1% to 12% of all cancer patients have a mutation in HER2 kinase in the United States and that approximately 7% to 9% of all estrogen receptor positive metastatic breast cancer patients who have received prior endocrine treatment have a mutation in HER2 kinase (approximately 8,000 to 10,000 patients in the United States).

**Neratinib**

Neratinib is a potent irreversible 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 breast cancer. 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 been previously treated with these existing treatments, most notably due to its irreversible inhibition of the HER2 target enzyme.

In addition, we believe neratinib has clinical application in the treatment of several other cancers as well, including other tumor types that over-express or have a mutation in HER2 or EGFR, such as breast cancer, cervical cancer, lung cancer or other solid tumors.

Our initial focus is on the commercialization and development of the oral formulation of neratinib.

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

*Extended Adjuvant Breast Cancer*

In 2017, the 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 adjuvant trastuzumab-based therapy. In 2018, the EC granted marketing authorization for NERLYNX in the EU for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. These approvals were obtained based on the two-year data obtained in our ExteNET trial.

*Two-Year ExteNET Data.* In July 2014, we announced top line results from our ExteNET trial, a Phase III clinical trial of neratinib for the extended adjuvant treatment of early stage HER2-positive breast cancer. The data from this trial were presented in an oral presentation at the American Society of Clinical Oncology ("ASCO") Annual Meeting in June 2015 and were published online in *The Lancet Oncology* in February 2016. The ExteNET trial was 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 (one 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.

The primary endpoint of the ExteNET 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 two-year DFS rate for the neratinib arm was 93.9% and the two-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 two-year DFS-DCIS rate for the neratinib arm was 93.9% and the two-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 two-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 two-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 two-year DFS-DCIS rate for the centrally confirmed patients in the neratinib arm was 94.7% and the two-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 two-year DFS rate for the neratinib arm was 95.4% and the two-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 two-year DFS rate for the centrally confirmed patients in the neratinib arm was 97.0% and the two-year DFS rate for centrally confirmed patients in the placebo arm was 88.4%.

*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 five-year invasive disease-free survival ("iDFS"), analysis as a follow-up to the primary two-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 five-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, or 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 five-year iDFS-DCIS rate for the neratinib arm was 89.7% and the five-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 five-year iDFS rate for the neratinib arm was 91.2% and the five-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 results of the ExteNET trial showed that after two years of follow-up, for patients with hormone receptor positive, HER2-positive early stage breast cancer patients who were treated within one year after the completion of trastuzumab based adjuvant therapy, iDFS was 95.3% in the patients treated with neratinib compared with 90.8% in those receiving placebo (hazard ratio = 0.49; 95% CI: (0.30, 0.78); p=0.002).

The safety results were unchanged from the primary two-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 (one patient, or 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.

In October 2020, we announced that efficacy results of neratinib in HER2-positive, hormone receptor-positive, or HR+, early stage breast cancer, ("eBC") from the Phase III ExteNET trial were published in *Clinical Breast Cancer*. The manuscript presented data focusing on HR+ patients who initiated treatment within a year of completing an adjuvant trastuzumab containing treatment (HR+ /< 1 yr) and subgroups of clinical interest including patients who did not achieve a pathological complete response (no pCR) after neoadjuvant treatment and therefore were at a high risk of disease recurrence (HR+/ <1 yr, no pCR). In the HR+ /< 1 yr patient population, the absolute 5-year invasive disease-free survival benefit versus placebo was 5.1% (HR=0.58, 95% CI 0.41–0.82) and absolute 8-year overall survival benefit was 2.1%. (HR=0.79, 95% CI 0.55–1.13). The 5-year cumulative incidence of central nervous system (CNS) metastases was 0.7% in the neratinib arm and 2.1% in the placebo arm.

In the HR+/ <1 yr, no pCR subgroup of patients that were at a high risk of disease recurrence the absolute 5-year iDFS benefit in the neratinib arm versus placebo was 7.4% (HR=0.60; 95% CI 0.33–1.07) and the 8- year overall survival benefit was 9.1% (HR=0.47; 95% CI 0.23– 0.92).

NERLYNX is currently in the body of the National Comprehensive Cancer Network ("NCCN") breast cancer guidelines for the treatment of adjuvant HER2-positive Breast Cancer (BINV-L) under the heading Useful in Certain Circumstances, with a recommendation for considering extended adjuvant neratinib for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence.

*CONTROL*. In February 2015, we initiated the CONTROL trial which is an international, open-label, Phase II study investigating the use of antidiarrheal prophylaxis or dose escalation in the prevention and reduction of neratinib-associated diarrhea and, more specifically, 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.

In December 2019 and December 2020, interim results from the CONTROL trial were presented at the 2019 CTRC-AACR San Antonio Breast Cancer Symposium, and the 2020 CTRC-AACR San Antonio Breast Cancer Symposium, respectively, and in December 2021, final results from the CONTROL trial were presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

Final results showed the incidence of grade 3 diarrhea for the 137 patients who received the loperamide prophylaxis was 31%, the incidence of grade 3 diarrhea for the 64 patients who received the combination of loperamide plus budesonide was 28%, the incidence of grade 3 diarrhea for the 136 patients who received the combination of loperamide plus colestipol was 21%, the incidence of grade 3 diarrhea for the 104 patients who received colestipol alone with loperamide as needed was 33%, the incidence of grade 3 diarrhea for the 60 patients who used the dose escalation 1 regimen (DE 1) was 13%, and the incidence of grade 3 diarrhea for the 62 patients who used dose escalation regimen 2 (DE 2) was 27%. Further information is provided in Table 1 below:

Table 1: Incidence of Treatment-Emergent Diarrhea

| | **Loperamide (N=137)** | **Budesonide (N=64)** | **Colestipol (N=136)** | **Colestipol + Loperamide Loperamide PRN (N=104)** | **Neratinib Dose Escalation (N=60)** | **Neratinib Dose Escalation Scheme 2 (N=62)** |
|---|---|---|---|---|---|---|
| Patient incidence of diarrhea by worst grade - n (%) | | | | | | |
| Any grade | 109 (80) | 55 (86) | 113 (83) | 99 (95) | 59 (98) | 61 (98) |
| Grade 1 | 33 (24) | 15 (23) | 38 (28) | 34 (33) | 24 (40) | 23 (37) |
| Grade 2 | 34 (25) | 22 (34) | 47 (35) | 31 (30) | 27 (45) | 21 (34) |
| Grade 3 | 42 (31) | 18 (28) | 28 (21) | 34 (33) | 8 (13) | 17 (27) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea leading to discontinuation | 28 (20) | 7 (11) | 5 (4) | 8 (8) | 2 (3) | 4 (6) |
| Hospitalization (due to diarrhea) | 2 (1) | 0 | 0 | 0 | 0 | 0 |

Adoption of neratinib dose escalation at the initiation of treatment, particularly the 2-week DE schedule ("DE1"), most markedly reduced the incidence, severity, and duration of neratinib-associated grade 3 diarrhea in CONTROL compared to other treatment cohorts. Both DE strategies showed a lower incidence of grade 3 diarrhea (DE1 13%; DE2 27%) compared with that observed in the ExteNET trial (historical control: 39.8%). No grade 4 diarrhea was reported in any cohort. The median cumulative duration of grade 3 diarrhea ranged from 2 – 2.5 days across the CONTROL DE study cohorts for the entire 12-month treatment period (compared with 5.0 days for ExteNET). The proportion of patients discontinuing neratinib because of diarrhea was decreased both DE cohorts (DE1 3%; DE2 6%) compared with ExteNET (17%). The adoption of neratinib DE + loperamide PRN during the first 2 weeks of treatment (DE1 cohort) was associated with the lowest rate of grade 3 diarrhea during the trial compared with all other anti-diarrheal strategies investigated in CONTROL. These final findings from the CONTROL study showed improved tolerability of neratinib with all diarrhea prophylaxis strategies and suggest that neratinib DE1 with loperamide PRN may allow patients to stay on treatment longer and receive the full benefit of neratinib therapy.

This study is complete, and the results have been submitted to multiple global Health Authorities to support the addition of a dose escalation regimen to approved package inserts. As of December 31, 2021, label changes to incorporate dose escalation had been approved in the US, Canada and Australia.

***PB272 (neratinib, oral)—Metastatic Breast Cancer***

On February 25, 2020, the FDA approved our supplemental New Drug Application ("NDA") for the use of neratinib in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This approval was based on the results from our NALA trial.

*Trials of Neratinib as a Single Agent*. In 2009, Pfizer Inc. ("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.

Data from a second 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.

*NALA.* In February 2013, we reached agreement with the FDA under a Special Protocol Assessment ("SPA") for our Phase III clinical trial (PUMA-NER-1301 or the NALA trial) of neratinib in patients with HER2-positive metastatic breast cancer who have failed two or more prior treatments (third-line disease). An SPA is a written agreement between the trial's sponsor and the FDA regarding the design, endpoints, and planned statistical analysis of the Phase III trial with respect to the effectiveness of PB272 for the indication to be studied to support a New Drug Application ("NDA"). The European Medicines Agency ("EMA") also provided follow-on Scientific Advice ("SA") consistent with that of the FDA regarding our Phase III trial design and endpoints used for such design to support the submission of an marketing authorization application ("MAA") in the EU.

Pursuant to the SPA and SA, the Phase III NALA trial was designed as a randomized controlled trial of neratinib plus capecitabine versus Tykerb® (lapatinib) plus capecitabine in patients with third-line HER2-positive metastatic breast cancer. The trial enrolled 621 patients who were randomized (1:1) to receive either neratinib plus capecitabine or lapatinib plus capecitabine. The trial was conducted globally at sites in North America, Europe, Asia-Pacific and South America. The co-primary endpoints of the trial were centrally confirmed PFS and overall survival, or OS. An alpha level of 1% was allocated to the PFS and 4% allocated to OS.

In June 2019, we announced that results from the Phase III NALA trial were presented at the ASCO 2019 Annual Meeting in Chicago. For the primary analysis of centrally confirmed PFS, treatment with neratinib plus capecitabine resulted in a statistically significant improvement in centrally confirmed PFS (hazard ratio=0.76, p=0.0059) compared to treatment with lapatinib plus capecitabine. Because the hazard ratio was found to not be constant over time (i.e., the proportional hazard assumption did not hold), the statistical analysis plan for the NALA trial prespecified that a restricted means survival analysis at 24 months would be performed. In this prespecified analysis the mean PFS for the patients treated with neratinib plus capecitabine was 8.8 months and the mean PFS for the patients treated with lapatinib plus capecitabine was 6.6 months.

For the primary analyses of OS, neratinib plus capecitabine resulted in an improvement in OS that, although not statistically significant, trended numerically in favor of the neratinib plus capecitabine arm of the study (hazard ratio = 0.88, p=0.21). The median OS for the patients treated with neratinib plus capecitabine was 21.0 months and the median OS for the patients treated with lapatinib plus capecitabine was 18.7 months. In the prespecified restricted means analysis the mean

OS at 48 months for the patients treated with neratinib plus capecitabine was 24.0 months and the mean OS for the patients treated with lapatinib plus capecitabine was 22.2 months.

For the secondary endpoint of time to intervention for symptomatic central nervous system disease (also referred to as brain metastases), the results of the trial showed that treatment with neratinib plus capecitabine led to an improvement over the combination of lapatinib plus capecitabine. The overall cumulative incidence of CNS metastases was 22.8% for the neratinib plus capecitabine arm and 29.2% for the lapatinib plus capecitabine arm (p=0.043). For the secondary endpoint of duration of response, neratinib plus capecitabine treatment resulted in a longer duration of response compared to lapatinib and capecitabine treatment, with a median response of 8.54 months compared to a median response of 5.55 months (HR = 0.495, p = 0.0004).

Treatment-emergent adverse events ("TEAEs") were similar between arms: TEAEs leading to neratinib/lapatinib discontinuation were lower with neratinib (10.9%) than with lapatinib (14.5%). There was a higher rate of grade 3 diarrhea with neratinib plus capecitabine compared to lapatinib plus capecitabine (24.4% vs 12.5%); however, the discontinuations due to diarrhea (neratinib plus capecitabine: 2.6%, lapatinib plus capecitabine: 2.3%) were similar in both arms.

In the NCCN Breast guidelines for HER2 positive unresectable or Stage IV (M1) disease, neratinib + capecitabine is currently listed as a treatment option for the third line and beyond setting (BINV-Q).

*Metastatic Breast Cancer with Brain Metastases*

Approximately one-half of the patients with HER2-positive metastatic breast cancer develop metastases that spread to their brain. The current antibody-based treatments, including trastuzumab and pertuzumab, do not enter the brain and therefore are not believed to be effective in treating these patients.

Neratinib is currently being tested in a clinical trial in collaboration with Translational Breast Cancer Research Consortium referred to as TBCRC 022. The purpose of this study is to determine how well neratinib works in treating breast cancer that has spread to the brain. In this research study, the investigators are looking to see how well neratinib works to decrease the size of or stabilize breast cancer that has metastasized to the brain.

In June 2017, we presented interim data from the TBCRC 022 at the ASCO 2017 Annual Meeting. The multicenter Phase II clinical trial enrolled patients with HER2-positive metastatic breast cancer who have brain metastases. 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.

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

The primary endpoint of the trial was CNS Objective Response Rate according to a composite criteria that included volumetric brain MRI measurements, steroid use, neurological signs and symptoms, and Response Evaluation Criteria in Solid Tumors ("RECIST") evaluation for non-CNS sites. The secondary endpoint of the trial was CNS response by Response Assessment in Neuro-Oncology-Brain Metastases, or 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.

The TBCRC 022 trial is currently enrolling patients in an arm of the study that is administering neratinib 160 mg daily in combination with the drug ado-trastuzumab emtansine (T-DM1, Kadcyla) in patients with HER2-positive metastatic breast cancer that has metastasized to the brain. Data from this trial is expected in 2022.

In April 2018, we announced that NERLYNX has been included as a recommended treatment option in the latest NCCN, Clinical Practice Guidelines in Oncology Central Nervous System Cancers for Breast Cancer patients with brain metastases. The NCCN designated NERLYNX in combination with capecitabine as a category 2B treatment option and NERLYNX in combination with paclitaxel as a category 2B treatment option. Use, as designated for breast cancer patients with brain metastases, is outside the FDA-approved indication for NERLYNX and considered investigational, and we do not market or promote NERLYNX for these uses.

***PB272 (neratinib, oral)—Other Potential Applications***

*HER2 Mutation-Positive Solid Tumors*

Based on the results from the Cancer Genome Atlas Study, we estimate that between 1% and 12% of each solid tumor has a mutation in HER2.

*SUMMIT -- 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, which we refer to as the 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 HER mutations.

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 and were published in January 2018 in *Nature*. 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.

The interim safety results observed in the SUMMIT study were consistent with that observed previously in metastatic patients with HER2 amplified tumors. With anti-diarrheal prophylaxis and management, diarrhea has not been 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 as of March 10, 2017, 31 patients (22%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for those patients was two days. Four 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.

*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.

In December 2020, we announced that updated interim results from the SUMMIT basket trial in the HER2-mutant, hormone receptor positive breast cancer cohort were presented at the San Antonio Breast Cancer Symposium. In the HER2-mutant, hormone receptor (HR)-positive breast cancer cohort, 51 patients received 240 mg of neratinib daily in combination with trastuzumab and fulvestrant. In this cohort, patients had received a median of four prior lines of therapy in the metastatic setting (range 1-10 prior regimens) before entering the trial. 36 patients (70.6%) had received prior fulvestrant, 35 patients (68.6%) had received prior aromatase inhibitor and 4 patients (7.8%) had received prior tamoxifen. Further, 30 patients (58.8%) received prior cyclin-dependent kinase 4/6-inhibitor (CDK4/6i) therapy. Thirty-five patients (68.6%) had received prior chemotherapy.

The interim efficacy summary of the breast cohort that received neratinib in combination with trastuzumab and fulvestrant showed that for the 37 RECIST efficacy evaluable patients, 17 patients (45.9%) experienced a confirmed objective response, including one complete response (2.7%) and 16 (43.2%) partial responses, and 20 patients (54.1%) experienced clinical benefit (clinical benefit is defined as confirmed complete response or partial response or stable disease for at least 24 weeks). The median duration of response was 10.9 months and the median progression-free survival was 8.3 months.

The safety profile observed in patients treated with the combination of neratinib plus trastuzumab plus fulvestrant in the SUMMIT study was consistent with that observed previously in metastatic patients with HER2 amplified tumors. All patients received anti-diarrheal prophylaxis with loperamide alone. The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. For the 51 safety evaluable patients enrolled in this cohort, 20 patients (39.2%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for those patients was 6 days. No patient permanently discontinued neratinib due to diarrhea.

In December 2021, we announced updated interim results from the SUMMIT basket trial in the HER2-mutant, hormone receptor ("HR")-positive, metastatic breast cancer cohort and a separate cohort of patients with metastatic triple negative breast cancer at the San Antonio Breast Cancer Symposium. In the HER2-mutant, HR-positive, metastatic breast cancer cohort, patients who have previously received CDK4/6 inhibitors were previously enrolled in a non-randomized cohort and received 240 mg of neratinib per day in combination with fulvestrant and trastuzumab. In the HER2-mutant, TNBC cohort, patients received 240 mg of neratinib per day in combination with trastuzumab. All patients received anti-diarrheal prophylaxis with loperamide alone for the first two treatment cycles.

Following our discussion with the FDA, the SUMMIT trial had been amended to randomize HR-positive, HER2-mutant metastatic breast cancer patients to receive either: (i) the combination of neratinib (N), trastuzumab (T) and fulvestrant (F), (ii) the combination of fulvestrant and trastuzumab, or (iii) fulvestrant alone. Once randomized, patients received either neratinib plus fulvestrant plus trastuzumab, fulvestrant plus trastuzumab, or fulvestrant in 1:1:1 ratio. All patients received anti-diarrheal prophylaxis with loperamide alone for the first two treatment cycles.

In the non-randomized cohort, for the 26 patients with HR-positive, HER2-mutated MBC who had previously received CDK4/6 inhibitors, the efficacy results showed that, as of a cutoff date of September 10, 2021, for the patients who received neratinib plus fulvestrant plus trastuzumab, 12 patients (46.2%) experienced a confirmed objective response, all of which were partial responses, and 15 patients (57.7%) experienced clinical benefit (clinical benefit is defined as confirmed complete response or partial response, or stable disease for at least 24 weeks). The median duration of response was 14.4 months and the median progression-free survival was 8.2 months as of the cutoff date (Table 2).

For the randomized portion of the trial, for the patients with HR-positive, HER2-mutated MBC who had previously received CDK4/6 inhibitors, no patient in either the fulvestrant plus trastuzumab or fulvestrant alone arm experienced a confirmed objective response. In the 7 randomized patients who received the combination of neratinib, trastuzumab and fulvestrant, as of the cutoff date, 2 patients (28.6%) experienced a confirmed objective response, including one complete response (14.3%) and one partial response (14.3%), and 2 patients (28.6%) experienced clinical benefit as of the cutoff date. The median duration of response was not reached and the median progression-free survival was 6.2 months as of the cutoff date (Table 2).

For all 33 patients with HR-positive, HER2-mutated MBC, who had previously received CDK4/6 inhibitors, who received the combination of neratinib plus trastuzumab plus fulvestrant, the efficacy results showed, as of the cutoff date, that 14 patients (42.4%) experienced a confirmed objective response, including one complete response (3.0%) and 13 partial responses (39.4%), and 17 patients (51.5%) experienced clinical benefit. The median duration of response was 14.4 months and the median progression-free survival was 7.0 months as of the cutoff date (Table 2).

Following review by the Independent Data monitoring committee, the fulvestrant plus trastuzumab and fulvestrant only arms were closed to enrolment and additional patients enrolled to receive the combination of neratinib, trastuzumab and fulvestrant to further evaluate the efficacy of the combination. Enrolment in this cohort is now complete and no additional patients are being enrolled.

**Table 2: Efficacy findings from HR+ MBC patients**

| | Non-randomized (N+F+T, n=26) | Randomized (N+F+T, n=7) | Randomized (F+T, n=7) | Randomized (F, n=7) | All N+F+T (N+F+T, n=33) |
|---|---|---|---|---|---|
| Objective response (confirmed CR/PR)[a], n (%)... | 12 (46.2) | 2 (28.6) | 0 | 0 | 14 (42.4) |
| CR..... | 0 | 1 (14.3) | 0 | 0 | 1 (3.0) |
| PR..... | 12 (46.2) | 1 (14.3) | 0 | 0 | 13 (39.4) |
| Best overall response (confirmed or unconfirmed PR or CR), n (%) ..... | 15 (57.7) | 3 (42.9) | 0 | 0 | 18 (54.5) |
| Median DOR[b], months (95% CI)..... | 14.4 (6.4–NE) | NE | NE | NE | 14.4 (6.4–NE) |
| Clinical benefit[c], n (%) ..... | 15 (57.7) | 2 (28.6) | 0 | 0 | 17 (51.5) |
| Median PFS, months (95% CI)..... | 8.2 (4.0–15.1) | 6.2 (2.1–NE) | 3.9 (1.9–4.1) | 4.1 (1.6–4.1) | 7.0 (4.2–12.7) |
| Median duration of treatment, months (range) .... | 8.7 (1.0–22.1) | 5.0 (0.7–13.2) | 3.5 (0.8–4.1) | 2.1 (0.7–4.1) | 6.5 (0.7–22.1) |

Note: Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1) for HR+ cohorts

CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival

[a] Objective response defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met

[b] Kaplan-Meier analysis

[c] Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

Based on the results from the randomized portion of the trial, for patients with hormone receptor-positive, HER2-mutant metastatic breast cancer, the Independent Data Monitoring Committee recommended closing enrollment to the fulvestrant plus trastuzumab and fulvestrant alone arms of the trial and recommended continuing enrollment in the neratinib plus trastuzumab plus fulvestrant arm of the trial. As of the cutoff date, the Company has enrolled 19 additional patients in this triplet arm of the trial.

For the 18 patients with HER2-mutant TNBC who received fulvestrant plus trastuzumab, as of the cutoff date, 6 patients (33.3%) experienced a confirmed objective response, including one complete response (5.6%) and 5 partial responses (27.8%), and 7 patients (38.9%) experienced clinical benefit (clinical benefit is defined as confirmed complete response or partial response or stable disease for at least 24 weeks). The median duration of response was not reached and the median progression-free survival was 6.2 months as of the cutoff date. (Table 3).

**Table 3: Efficacy findings from TBNC patients**

| | TNBC (N + T, n=18) |
|---|---|
| Objective response (confirmed CR/PR)[a], n (%) | 6 (33.3) |
| CR | 1 (5.6) |
| PR | 5 (27.8) |
| Best overall response (confirmed or unconfirmed PR or CR), n (%) | 7 (38.9) |
| Median DOR[b], months (95% CI) | NE |
| Clinical benefit[c], n (%) | 7 (38.9) |
| Median PFS, months (95% CI) | 6.2 (2.1-8.2) |
| Median duration of treatment, months (range) | 4.4 (0.3-15.4) |

Note: Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1 or modified PERCIST) for
TBNC cohorts; TNBC cohort analysis ongoing CR, confirmed response; PR, partial response; CL, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival

[a] Objective response defined as either a complete or partial response that is confirmed no less than 4 - weeks after the criteria for responses
are initially met

[b] Kaplan-Meier analysis

[c] Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥ 24 weeks (within +/- 7 day visit window)

***EGFR Exon 18 Mutated Non Small Cell Lung Cancer***

Exon 18 mutations comprise approximately 5% of the EGFR mutations detected in lung cancer. Pre-clinical data have demonstrated that neratinib was active in pre-clinical models of EGFR exon 18 mutated lung cancer and neratinib was previously shown to be active in treating patients with exon 18 mutated lung cancer in a Phase II trial that was published in the *Journal of Clinical Oncology* in 2010.

In November 2020, we announced interim results from the ongoing SUMMIT trial of neratinib in the cohort of metastatic non-small cell lung cancer ("NSCLC") patients with EGFR exon 18 mutations who have been previously treated with an EGFR targeted TKI. In the EGFR exon 18 mutation cohort, patients with lung cancer with single or complex EGFR exon 18 mutations, who were EGFR TKI naïve or were previously exposed to EGFR TKI, were enrolled into this study and received 240 mg of neratinib daily as a single agent.

In this cohort of 11, patients had received a median of two prior lines of therapy in the metastatic setting (range 1-3 prior regimens) before entering the trial. Ten patients had been previously treated with an EGFR targeted TKI (gefitinib, erlotinib, osimertinib and/or afatinib).

The interim efficacy results from the trial showed that for the 10 evaluable patients who had been treated with a prior EGFR TKI, six patients (60%) experienced a partial response, which included four patients (40%) with a confirmed partial response. Eight patients (80%) experienced clinical benefit (clinical benefit is defined as confirmed complete response or partial response or stable disease for at least 16 weeks). The median duration of response was 7.5 months and the median progression free survival was 9.1 months. The success criteria for both the first stage and the second stage of the Simon's 2-stage design were met and enrollment in the second stage of this cohort continues.

The safety profile observed in the subgroup of patients with EGFR exon 18 mutated NSCLC showed that for the 11 patients who received neratinib in the trial, there were no reports of grade 3 or higher diarrhea. Four patients (36%) reported grade 1 and one patient (9%) reported grade 2 diarrhea. No patients required a dose hold, dose reduction, hospitalization or permanently discontinued neratinib due to diarrhea.

This cohort is now closed to enrollment.

**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 ("GLP") and clinical testing in accordance with Good Clinical Practice standards ("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), and the national laws of the 27 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 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, Lilly, Takeda, Daiichi Sankyo and Seagen. Lilly is developing their drug abemaciclib, which acts via a different mechanism than neratinib, in patients with hormone receptor–positive, HER2-positive, node-positive, high-risk early breast cancer who have completed standard adjuvant HER2-targeted treatment. All of these competitors are developing their drugs for the treatment of early stage and/or metastatic HER2-positive breast cancer and/or for cancers that have a HER2 mutation. We are an early commercial 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**

We currently have a U.S. direct specialty sales force of approximately 38 sales specialists who are focused on promoting NERLYNX to oncologists. This sales force is supported by an experienced leadership team consisting of regional business leaders, as well as a commercial team 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 2018, the EC granted marketing authorization for NERLYNX in the EU for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. We plan to continue to pursue commercialization of NERLYNX in Europe and other countries outside the United States, where approved. To facilitate our international activities, we have entered into exclusive sub-license agreements with various parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved. We are currently party to several sub-licenses in various regions outside the United States, including Europe (excluding Russia and Ukraine), Australia, Canada, China, Southeast Asia, Israel, South Korea, and various countries and territories in Central and South America. As we expand into additional territories we will continue to evaluate whether we seek to commercialize NERLYNX in those territories directly or through additional sub-licenses.

**Intellectual Property and License Agreements**

We hold a worldwide exclusive license under our license agreement with Pfizer, as amended, or the Pfizer Agreement, to 21 granted U.S. patents and four pending U.S. patent applications, as well as foreign counterparts thereof, and other patent applications and patents claiming priority therefrom to develop and commercialize certain compounds, including neratinib.

In the United States, we have a license to an issued patent, which is set to expire in 2030, for the composition of matter of neratinib, our lead compound. We also have a license to an issued U.S. patent for the use of neratinib in the treatment of breast cancer, which is currently set to expire in 2025, 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, two issued patents for the use of neratinib in combination with capecitabine the later of which is set to expire in 2031 and two issued patents for the formulation of NERLYNX that are set to expire in 2030, two issued patents for the polymorphic forms of neratinib which are set to expire in 2028, one issued patent for the preparation of the polymorphic forms of neratinib which is set to expire in 2028, and three issued patents for the use of the polymorphic forms of neratinib in the treatment of breast cancer which are set to expire in 2028. In jurisdictions which permit such, we will seek patent term extensions where possible for certain of our patents (discussed further below, including in “Government Regulation”). We plan to pursue additional patents in and outside the United States from the four pending U.S. patent applications noted above and the 67 pending foreign patent applications, respectively, covering neratinib composition, formulations, and combinations and uses thereof, and additional therapeutic uses of neratinib. In addition, we will pursue patent protection for any new discoveries or inventions made in the course of our development of neratinib.

In the United States, marketing approval for neratinib was obtained on July 17, 2017, which provided five years of regulatory exclusivity. Marketing approval in the United States for neratinib in combination with capecitabine was obtained on February 25, 2020, which provided three years of regulatory exclusivity. Requests for patent term extension under the Hatch-Waxman Act have been filed for two patents in the United States: U.S. Patent No. 7,399,865 and U.S. Patent No. 9,211,291. We elected to apply patent term extension to U.S. Patent No. 7,399,865. The U.S. Patent and Trademark Office ("USPTO") has determined that U.S. Patent No. 7,399,865 is eligible for five years of patent term extension. Once extended, U.S. Patent No. 7,399,865 will expire December 29, 2030. See “Government Regulation” below. If we obtain marketing approval in the United States for new uses or combinations therapies for neratinib, we may be eligible for additional periods of regulatory exclusivity, such as three-year market exclusivity covering the new use. If we obtain market approval for neratinib or other drug candidates or in certain jurisdictions outside the United States, we may be eligible for regulatory protection, such as, eight to eleven years of data and marketing exclusivity potentially are available for new drugs in the EU; 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. In Europe, marketing approval for neratinib was obtained on August 31, 2018, which provided 10 years of regulatory exclusivity. Between 2019 and 2020, marketing approval for neratinib was obtained in Argentina, Brunei, Canada, Chile, China, Ecuador, Hong Kong, Israel, Malaysia, Singapore and Taiwan. Where available and eligible, regulatory or data exclusivity has been obtained, or is currently being pursued in these jurisdictions outside the United States and Europe. Patent term extension or supplemental protection certificate are being, or will be, pursued in jurisdictions where available and eligible, including Chile, Europe and Taiwan. Current market approved jurisdictions where patent term extensions or supplemental protection certificates are not available, not eligible, or not pursued, include Argentina, Brunei, Canada, China, Ecuador, Hong Kong, Israel, Malaysia and Singapore. 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.

On November 28, 2011, a Boehringer Ingelheim entity filed an opposition to European Patent No. EP1848414, which was licensed from Pfizer in 2011, and which included specific claims to 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. Oral proceedings were held before the Opposition Division of the European Patent Office in Munich, Germany on February 4, 2014. The decision of the Opposition Division was to uphold the granted claims of the European patent that relate to the T790M mutation without any modification. This included specific claims to a 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. Both parties appealed this decision. The opposition was rejected as inadmissible by the Board of Appeal of the European Patent Office on December 1, 2020, and the EP1848414 patent was upheld as originally granted. We have filed Supplemental Protection Certificate applications in the countries the EP1848414 patent was validated. Of these applications, five have been granted, and the remaining are in active prosecution.

An Opposition was filed by Hexal AG ("Hexal") on August 3, 2016 against European Patent No. EP2416774 which was licensed from Pfizer in 2011, and which claims neratinib for use in a method for treating HER-2/neu overexpressed/amplified cancer and improving IDFS, wherein the method comprises delivering neratinib therapy to HER-2/neu overexpressed/amplified cancer patients following the completion of at least one year of trastuzumab adjuvant therapy, and wherein the neratinib therapy comprises treating the cancer patients with neratinib for at least twelve months. An oral hearing was held December 8, 2017, wherein the patent was maintained as granted. Following an appeal filed by Hexal, the Board of Appeal of the European Patent Office rejected the claims as granted and all pending auxiliary requests during the oral hearing of September 2, 2021. Before issuance of a decision, we withdrew approval of the text in which the patent was granted and all pending auxiliary requests, thereby revoking the patent and concluding the appeal.

On October 4, 2017, Hexal also filed an Opposition to European Patent No. EP2326329 which was licensed from Pfizer in 2011, and which claims a combination of neratinib and pharmaceutically acceptable salts thereof with capecitabine for use in a method of treating an Erb-2 positive metastatic breast cancer. An oral hearing was held on February 13, 2019, wherein the patent was maintained as granted. Hexal then appealed, which appeal is pending.

On May 21, 2020, Hexal also filed an Opposition to European Patent No. EP2498756, which was licensed from Pfizer in 2011, and which claims, inter alia, tablet formulations of neratinib maleate comprising intragranular and extragranular components. Oral hearings have been re-scheduled for April 8, 2022 and briefings exchange between the parties are still in progress.

An Opposition was filed by Generics (UK) Ltd. ("Generics") on September 3, 2015 against European Patent No. EP2656844, which was licensed from Pfizer in 2011, and which claims, inter alia, a pharmaceutical pack containing 50 to 300 mg of neratinib and pharmaceutically acceptable salts thereof and vinorelbine for use in a method of treating a neoplasm. An oral hearing was held July 3, 2017, wherein the patent was maintained as granted. Generics then appealed. The appeal was dismissed by the Board of Appeal of the European Patent Office on August 11, 2020, and the EP2656844 patent was upheld as originally granted.

Unipharm filed a pre-grant opposition to Israeli Patent Application No. IL210616 on January 31, 2016. This application was licensed from Pfizer in 2011. An oral hearing was held in Jerusalem before the Israeli Patent Office on January 22, 2018. The patent was granted by the Israeli Patent Office upon filing of amendments to the claims. No opposition to the patent has been filed within the allowed opposition period. The granted claims are directed to use of a combination of neratinib and capecitabine in the manufacture of a medicament for treating a neoplasm.

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**

We license the worldwide exclusive rights for the development, manufacture and commercialization of neratinib (oral), neratinib (intravenous), PB357, and certain related compounds from Pfizer Inc., or Pfizer. Under the Pfizer agreement, Pfizer was obligated to transfer to us certain information, records, regulatory filings, materials and inventory controlled by Pfizer 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 were obligated to continue such studies pursuant to an approved development plan, including after the license agreement terminates for reasons unrelated to Pfizer's breach of the license agreement, subject to certain specified exceptions. We were 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, Pfizer was obligated to 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. In July 2021, we entered into a confirmatory agreement with Pfizer and Wyeth LLC, or Wyeth, confirming that the rights granted to us by Pfizer under the Pfizer Agreement included Wyeth's rights in neratinib (oral), neratinib (intravenous), PB357, and certain related compounds.

As consideration for the license, we are required to make payments totaling $187.5 million upon the achievements of certain milestones if all such milestones are achieved. FDA approval of NERLYNX in July 2017 triggered a one-time milestone payment. In June 2020, we entered into a letter agreement ("Letter Agreement") with Pfizer relating to the method of payment associated with a one-time milestone payment under the Pfizer Agreement. The Letter Agreement permits us to make the milestone payment in installments with portions of the amount payable to Pfizer (including interest) made in June and November 2020 for approximately $20.6 million in the aggregate and the remaining portion to be made in September 2021 for approximately $21.9 million. Unpaid portions of the milestone payment will accrue interest at 6.25% per annum until paid. The installment payments and accrued interest are included in accrued in-licensed rights on the accompanying consolidated balance sheets.

The Pfizer Agreement originally stipulated that should we commercialize any of the compounds licensed from Pfizer or any products containing any of these compounds, we will be obligated to pay to Pfizer 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, we signed an amendment to the Pfizer Agreement that, among other things reduced the annual royalties to be paid on net sales of licensed products from a tiered royalty rate structure ranging between 10% to 20% to a fixed rate in the low to mid-teens.

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. We can terminate the Pfizer Agreement at will at any time or for safety concerns, in each case upon specified advance notice. Each party may terminate the Pfizer Agreement if the other party fails to cure any breach of a material obligation by such other party within a specified time period. Pfizer may terminate the Pfizer agreement in the event of our bankruptcy, receivership, insolvency or similar proceeding. The Pfizer agreement contains other customary clauses and terms as are common in similar agreements in the industry.

**Sub-License Agreements**

*Specialised Therapeutics Agreement*

On November 20, 2017, we entered into a sub-license agreement, or the Specialised Therapeutics Agreement, with Specialised Therapeutics Asia Pte Ltd. ("STA"). Pursuant to the Specialised Therapeutics Agreement, we granted to STA, under certain of our intellectual property rights relating to neratinib, an exclusive, sublicensable (under certain circumstances) license to commercialize any pharmaceutical product containing neratinib in finished form for the extended adjuvant treatment of 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 entered into between the parties.

Pursuant to the Specialised Therapeutics Agreement, we received an upfront payment and will potentially receive additional regulatory milestone payments. In addition, we will receive double-digit royalties on sales of licensed products, calculated as a percentage of net sales of licensed products throughout 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.

*Medison Agreement:*

During the first quarter of 2018, we entered into a sub-license agreement, or the Medison Agreement, with Medison Pharma Ltd., or Medison. Pursuant to the Medison Agreement, we granted to Medison, under certain of our intellectual property rights relating to neratinib, an exclusive license to commercialize neratinib and certain related compounds and participate in the named patient supply in Israel, or the Medison Territory, subject to the terms of the Medison Agreement and the related supply agreement. Pursuant to the Medison Agreement, we will potentially receive milestone payments due to us upon successful completion of certain separate, distinct performance obligations. In addition, we are entitled to receive double-digit royalties on sales of licensed products, calculated as a percentage of net sales of licensed products in the Medison Territory.

*Pint Agreement*

On March 30, 2018, we entered into a sub-license agreement, or the Pint Agreement, with Pint Pharma International SA, or Pint. Pursuant to the Pint Agreement, we granted to Pint, under certain of our intellectual property rights relating to neratinib, an exclusive, sublicensable (under certain circumstances) license to develop and commercialize any product containing neratinib and certain related compounds in Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama, Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela, French Guiana, the Falkland Islands, and Mexico, or the Pint Territory.

The Pint Agreement sets forth the parties' respective obligations with respect to the development, commercialization, and supply of the licensed product. Pint will, at its expense, develop the licensed product for the purpose of obtaining regulatory approval in the Pint Territory, subject to our consent to conduct such development activities and approval of certain aspects of clinical studies conducted by Pint. Within the Pint Territory, Pint will also be responsible for regulatory and commercialization activities. 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, subject to certain exceptions therein.

Pursuant to the Pint Agreement, we received an upfront payment and will potentially receive additional regulatory and sales-based milestone payments. In addition, we are entitled to receive double-digit royalties on sales of licensed products, calculated as a percentage of net sales of licensed products throughout the Pint Territory.

The term of the Pint Agreement continues, on a country-by-country basis, until the later of (i) the expiration or abandonment of the last licensed patent covering the licensed product in such country, 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 Pint 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. Pint may also terminate the Pint Agreement at will, for certain safety concerns.

*Knight Agreement*

On January 9, 2019, we entered into a sub-license agreement, or the Knight Agreement, with Knight Therapeutics, Inc., or Knight. Pursuant to the Knight Agreement, we granted to Knight, under certain of the our intellectual property rights relating to neratinib, an exclusive, sublicensable (under certain circumstances) license (i) to commercialize any product containing neratinib and certain related compounds in Canada, or the Knight Territory, (ii) to seek and maintain regulatory approvals for the licensed products in the Knight Territory and (iii) to manufacture the licensed products anywhere in the world solely for the development and commercialization of the licensed products in the Knight Territory for human use, subject to the terms of the Knight Agreement and a supply agreement to be negotiated and executed by the parties.

Under the terms of the Knight Agreement, we will be solely responsible for the manufacturing and supply of the licensed products to Knight, but under limited circumstances Knight may obtain the right to manufacture the licensed products under the supply agreement.

The Knight Agreement sets forth the parties' respective obligations with respect to the commercialization of the licensed products. Within the Knight Territory, we will be solely responsible for obtaining the regulatory approval for the indication of extended adjuvant treatment of HER2-positive early stage breast cancer, or the Initial Indication, and Knight will use commercially reasonable efforts to prepare, file and manage regulatory filings for any other indications in the field of human use. Promptly after obtaining the regulatory approval for the Initial Indication in the Knight Territory, we will transfer such regulatory approval to Knight, and Knight will own and hold any regulatory approvals for the licensed products in the Knight Territory in its name.

Pursuant to the Knight Agreement, we received an upfront payment and will potentially receive additional regulatory and commercial milestone payments. In addition, we are entitled to receive double-digit royalties on sales of licensed products, calculated as a percentage of net sales of licensed products in the Knight Territory.

The term of the Knight Agreement continues, on a licensed product-by-licensed product basis, until the later of (i) the expiration or abandonment of the last valid claim of the licensed patents that covers such licensed product in the Territory, or (ii) the earlier of (a) the time when generic competitors to such licensed product have achieved a specified level in such country, or (b) ten (10) years following the date of first commercial sale of such licensed product in the Territory. The Knight 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.

*Pierre Fabre Agreement*

On March 29, 2019, we entered into a sub-license agreement, or the Pierre Fabre Agreement, with Pierre Fabre Medicament SAS, or Pierre Fabre. Pursuant to the Pierre Fabre Agreement, we granted to Pierre Fabre under certain of our intellectual property rights relating to neratinib an exclusive, sub-licensable (under certain circumstances) license to develop, manufacture and commercialize any pharmaceutical product containing neratinib for therapeutic and prophylactic

indications for human or veterinary use in European countries excluding Russia and Ukraine, along with countries in North Africa and francophone countries of West Africa, or the Pierre Fabre Territory. On November 25, 2019, we entered into a license amendment, or the First Pierre Fabre Amendment, with Pierre Fabre to extend Pierre Fabre's licensed territory to the Middle East, South Africa, Sudan and Turkey, or together with the Pierre Fabre Territory, the First Pierre Fabre Territory.

On February 24, 2021, we resolved a dispute with our former partner CANbridge Biomed Limited and terminated our sub-license agreement. Simultaneous to the termination of this agreement, we entered into a third license amendment (the "Third Pierre Fabre Amendment") with Pierre Fabre to further extend Pierre Fabre's licensed territory to Greater China, (the "Third Pierre Fabre Territory") which includes mainland China, Taiwan, Hong Kong and Macao (each a "China Region").

Pursuant to the Pierre Fabre Agreement, we received an upfront payment and will potentially receive additional regulatory and sales-based milestone payments based on regulatory and sales activities in the Licensee Territory (as such term is defined in the Third Pierre Fabre Amendment). Pursuant to the Third Pierre Fabre Amendment, we received an upfront payment of $50.0 million and will potentially receive, additional regulatory and sales-based milestone payments up to $240.0 million based solely on regulatory and sales activities in the Third Pierre Fabre Territory. In addition, we will receive double-digit royalties based on net sales of the licensed products in the Licensee Territory, on the one hand, and double-digit royalties based on net sales of the licensed products in the Third Pierre Fabre Territory, on the other hand. For the purposes of calculating royalties, sales of the licensed products in the Third Pierre Fabre Territory will be excluded from the sales of licensed products made in the Licensee Territory.

Under the terms of the Pierre Fabre Agreement, as amended, we are obligated to supply Pierre Fabre with the licensed products in accordance with the related supply agreement. Pierre Fabre will be responsible for conducting additional clinical studies and leading regulatory activities in connection with the EMA, and Greater China.

The term of the Pierre Fabre Agreement, as amended, continues until, on a country-by-country basis, the later of (i) the expiration or abandonment of the last licensed patent covering the licensed product in such country and (ii) the earlier of (a) the date upon which sales of generic versions of the licensed product reach a specified level in such country, or (b) the tenth anniversary of the first commercial sale of a licensed product in such country.

The Pierre Fabre Agreement, as amended, may be terminated by either party, in its entirety, if the other party commits a material breach, subject to a cure period, or if the other party is insolvent, and Pierre Fabre may terminate the Pierre Fabre Agreement, as amended, at its convenience or if there is evidence of safety issues with the licensed product. Pierre Fabre may terminate the Pierre Fabre Agreement, as amended, on a territory-by-territory basis, by terminating only the Licensee Territory or the Third Pierre Fabre Territory, for any of the foregoing reasons. We may terminate the Pierre Fabre Agreement, as amended, on a China Region-by-China Region basis or, under certain circumstances, in the entire Third Pierre Fabre Territory if Pierre Fabre is in material violation of certain anti-corruption laws.

*Bixink Agreement*

During the second quarter of 2020, we entered into a sub-license agreement, or the Bixink Agreement, with Bixink Therapeutics Co., Ltd. ("Bixink"). The Bixink Agreement granted intellectual property rights and set forth the respective obligations with respect to development, commercialization and supply of NERLYNX in South Korea, or the Bixink Territory. The Bixink Agreement includes potential milestone payments due to us upon successful completion of certain performance obligations, such as achieving regulatory approvals. In addition, we are entitled to receive double-digit royalties on sales of licensed products, calculated as a percentage of net sales of licensed products throughout the Bixink Territory.

**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.

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.

**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 ("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 requirements and other applicable regulations;
- submission to the FDA of an Investigational New Drug application ("IND") for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board ("IRB") or ethics committee at each clinical site before each trial may be initiated;
- 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 advisory committee review, if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the active pharmaceutical ingredient ("API") and finished drug product are produced and tested to assess compliance with current Good Manufacturing Practices ("cGMPs"); and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

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 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. Post-approval trials, sometimes referred to as Phase IV studies, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase IV clinical trials as a condition of approval of an NDA.

Furthermore, the sponsor, 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. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, such as in the circumstances where the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. In addition, some clinical trials are overseen by an independent group of qualified experts organized by the sponsor, known as a data safety monitoring board or committee. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial.

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 clinical testing, 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 consensus on the next phase of development. Sponsors typically use the end of a 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 submission of an NDA.

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, if the relevant data, assumptions, or information provided by the sponsor in a request for SPA change are found to be false statements or misstatements or omit relevant facts, or if the sponsor fails to follow the protocol that was agreed upon with the FDA. A documented SPA may be modified, and such modification will be deemed binding on the FDA review division, except under the circumstances described above, if FDA and the sponsor agree in writing to modify the protocol and such modification is intended to improve the study. 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.

The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. Under the Prescription Drug User Fee Act ("PDUFA") guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately

two months to make a “filing” decision after the application is submitted. The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to a filing review before the FDA accepts it for filing and substantive review.

The FDA also may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

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 and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs.

After the FDA evaluates an NDA, it will issue an approval letter ("Complete Response Letter"). An approval letter authorizes commercial marketing of the drug for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes the specific deficiencies in the NDA identified by the FDA and may require additional clinical data and/or additional 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.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA could 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. In addition, new government requirements, including those resulting from new legislation, may be established, or the FDA’s policies may change, which could impact the timeline for regulatory approval or otherwise impact ongoing development programs.

*Expedited Review and Approval Programs*. The FDA has various programs, including fast track designation, breakthrough therapy designation, priority review, and accelerated approval, which are intended to expedite or simplify the process for reviewing certain drugs and in the case of accelerated approval, provide for approval on the basis of surrogate or intermediate 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. Fast track designation, breakthrough therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

For example, fast track designation is designed to facilitate the development and expedite the review of drugs designed to treat serious or life-threatening diseases or conditions and which demonstrate the potential to address an unmet medical need for such diseases or conditions. Fast track designation applies to the combination of the product candidate and the specific indication for which it is being studied. The sponsor of a fast track product candidate has opportunities for more frequent interactions with the FDA review team during development. With regard to a fast track-designated product candidate, the FDA may also consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. .

A product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product candidate can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers.

Any product candidate submitted to the FDA for approval, including a product with a fast track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. An NDA is eligible for priority review if the product candidate is designed to treat a serious condition, and if approved, would provide a significant improvement in safety or effectiveness compared to available products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review. The FDA endeavors to review applications with priority review designations within six months of the filing date as compared to ten months for review of new molecular entity NDAs under its current PDUFA review goals.

Drug products intended for serious or life threatening conditions may be eligible for accelerated approval upon a determination that the product candidate 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 to verify or characterize the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Products receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required clinical trials in a timely manner, or if such trials fail to verify the predicted clinical benefit. In addition, the FDA currently requires pre-approval of promotional materials as a condition for accelerated approval.

*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.

The FDA closely regulates the marketing, labeling, advertising and promotion of drugs. A company can make only those claims relating to safety and efficacy that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

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 to one of the patents listed with the FDA by the holder of the NDA for the reference drug.

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 or from accepting and reviewing an application referencing the approved drug's application. 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 and clinical trials necessary to demonstrate safety and effectiveness.

*Foreign Regulation*

In addition to regulations in the United States, we may be subject to a variety of foreign regulations governing, among other things, 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 regulatory authorities of foreign countries before we may market products in those countries. 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.

*Non-clinical studies and clinical trials*

Similarly to the United States, the various phases of non-clinical and clinical research in the EU, are subject to significant regulatory controls.

Non-clinical studies are performed to demonstrate the health or environmental safety of new biological substances. Non-clinical studies must be conducted in compliance with the principles of GLP as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization ("ICH") guidelines on GCP as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If the sponsor of the clinical trial is not established within the EU, it must appoint an EU entity to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

The regulatory landscape related to clinical trials in the EU has been subject to recent changes. The EU Clinical Trials Regulation ("CTR") which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. Unlike directives, the CTR is directly applicable in all EU member states without the need for member states to further implement it into national law. The CTR notably harmonizes the assessment and supervision processes for clinical trials throughout the EU via a Clinical Trials Information System, which contains a centralized EU portal and database.

While the Clinical Trials Directive required a separate clinical trial application ("CTA") to be submitted in each member state, to both the competent national health authority and an independent ethics committee, much like the FDA and IRB respectively, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials whose CTA was made under the Clinical Trials Directive before January 31, 2022, the Clinical Trials Directive will continue to apply on a transitional basis for three years. Additionally, sponsors may still choose to submit a CTA under either the Clinical Trials Directive or the CTR until January 31, 2023 and, if authorized, those will be governed by the Clinical Trials Directive until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR. Medicines used in clinical trials must be manufactured in accordance with GMP. Other national and EU-wide regulatory requirements may also apply.

*Marketing Authorization*

In the EU, medicinal product candidates can only be placed on the market after obtaining a marketing authorization ("MA"). To obtain regulatory approval of a product candidate under EU regulatory systems, we must submit a MAA. The process for doing this depends, among other things, on the nature of the medicinal product. There are two types of MAs:

- "Centralized MAs" – are issued by the European Commission ("EC") through the centralized procedure, based on the opinion of the Committee for Medicinal Products for Human Use ("CHMP") of the EMA, and are valid throughout the EU. The centralized procedure is mandatory for certain types of products, such as (i) medicinal products, derived from biotechnology processes, such as genetic engineering, (ii) designated orphan medicinal products, (iii) advanced therapy medicinal products ("ATMPs") such as gene therapy, somatic cell therapy or tissue-engineered medicines, and (iv) medicinal products containing a new active substance indicated for the treatment of HIV/AIDS, cancer, neurodegenerative diseases, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EU or for product candidates which constitute a significant therapeutic, scientific or technical innovation; or for which the granting of an MA would be in the interest of public health in the EU.

- "National MAs" – are issued by the competent authorities of the EU member states, and only cover their respective territory and are available for product candidates not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in an EU member state, 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 EU assess the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. MA have an initial duration of five years. After these five years, the authorization may be renewed for an unlimited period on the basis of a reevaluation of the risk-benefit balance.

Under the centralized procedure, the maximum timeframe for the evaluation of a MAA by the EMA is 210 days. In exceptional cases, the CHMP might perform an accelerated review of a MAA in no more than 150 days (not including clock stops). Innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the U.S. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment but this is not guaranteed. The benefits of a PRIME designation include the appointment of a CHMP rapporteur before submission of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process.

*Data and Marketing Exclusivity*

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 or biosimilar product.

For example, the EU provides opportunities for market exclusivity. Upon receiving MA, reference medicinal products generally receive 8 years of data exclusivity and 10 years of market exclusivity. The data exclusivity period begins on the date of the product's first MA in the EU and prevents generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of 8 years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial MA of the reference product in the EU. The overall 10-year market exclusivity period can be extended to a maximum of 11 years if, during the first 8 years of those 10 years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity.

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.

*Post-Approval Requirements*

Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and/or the competent regulatory authorities of the member states. The holder of a MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports ("PSURs").

All new MAA must include a risk management plan ("RMP"), describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies.

The advertising and promotion of medicinal products is also subject to laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are

established under EU directives, the details are governed by regulations in each member state and can differ from one country to another.

Failure to comply with the aforementioned EU and member state laws may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials, or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

The aforementioned EU rules are generally applicable in the European Economic Area ("EEA") which consists of the 27 EU member states plus Norway, Liechtenstein and Iceland.

For other countries outside of the EU, UK and the United States, the requirements governing product development, the conduct of clinical trials, manufacturing, distribution, marketing approval, advertising and promotion, product licensing, pricing and reimbursement vary from country to country. Additionally, clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Additionally, to the extent that any of our product candidates, once approved, are sold in a foreign country, we may be subject to applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals.

***Coverage and Reimbursement***

In the United States and internationally, sales of 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 or future 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 changed the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, ACA established:

- 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.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the 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 2030, with the exception of a temporary suspension from May 1, 2020 through July 1, 2022 (with a 1% payment reduction from April 1 to June 30, 2022), 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. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, beginning January 1, 2024.

The cost of prescription pharmaceuticals in the United States has also been the subject of considerable discussion. There have been several Congressional inquiries, as well as legislative and regulatory initiatives and executive orders 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. Members of Congress and the Biden Administration have indicated they will continue to pursue legislative or administrative measures to control prescription drug costs, although the likelihood of such measures being adopted remains uncertain. For example, the Build Back Better Act, if enacted, would introduce substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, and the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D. If the Build Back Better Act is not enacted, similar or other drug pricing proposals could appear in future legislation. We cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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.

Similar political, economic and regulatory developments are occurring in the EU and may affect the ability of pharmaceutical companies to profitably commercialize their products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles. The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could restrict or regulate post-approval activities and affect the ability of pharmaceutical companies to commercialize their products. In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system and international healthcare systems. 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.

*Government Price Reporting*

Medicaid is a joint federal and state program for low-income and disabled beneficiaries. Medicare is a federal program covering individuals age 65 and over as well as those with certain disabilities. As a condition of having federal funds being made available for our covered outpatient drugs under Medicaid and Medicare Part B, we have enrolled in the Medicaid Drug Rebate Program ("MDRP"), which requires us to pay a rebate to state Medicaid programs for each unit of our covered outpatient drugs dispensed to a Medicaid beneficiary and paid for by a state Medicaid program. Medicaid drug rebates are based on pricing data that we must report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price ("AMP") for each drug and, in the case of our innovator products, the best price ("BP"). If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP.

Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. We participate in the 340B program, which is administered by the Health Resources and Services Administration ("HRSA"), and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered outpatient drugs used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and Medicare Part B and purchased by certain federal agencies and grantees, we also must participate in the U.S. Department of Veterans Affairs ("VA") Federal Supply Schedule ("FSS") pricing program. Under the VA/FSS program, we must report the Non-Federal Average Manufacturer Price ("Non-FAMP") for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non-FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). We must also pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information.

***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 and other regulatory agencies, 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 and similar requirements to the ones described above may apply in foreign jurisdictions. The requirements governing, among other things, marketing authorization and pricing and reimbursement vary widely from country to country.

***Other Healthcare Laws***

We are also subject to various federal, state and foreign laws pertaining to health care "fraud and abuse," including anti-kickback laws and false claims laws, data privacy and security laws and transparency laws.

The federal Anti-Kickback Statute ("AKS") prohibits, among other things, any person or entity from knowingly and willfully soliciting, receiving, offering or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of an item or service reimbursable, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" has been broadly interpreted to include anything of value. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution; however, these are drawn narrowly and require strict compliance in order to offer protection. Additionally, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

Federal civil and criminal false claims laws, such as the federal False Claims Act ("FCA") prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented false, fictitious or fraudulent claims for payment or approval by the federal government, including federal health care programs, such as Medicare and Medicaid, and knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim, or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. Private individuals can bring "qui tam" actions under the FCA, on behalf of the government and such individuals, commonly known as "whistleblowers," may share in amounts paid by the entity to the government in fines or settlement. Moreover, a claim including items or services resulting from a violation of the AKS constitutes a false or fraudulent claim for purposes of the FCA.

The federal Civil Monetary Penalties law 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.

The federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA") created 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. Like the AKS, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The federal transparency requirements under the Physician Payments Sunshine Act, created under the ACA, requires, among other things, certain manufacturers of drugs, devices, biologics and medical supplies reimbursed under Medicare, Medicaid, or the Children's Health Insurance Program to annually report to CMS information related to payments and other transfers of value provided to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician practitioners (nurse practitioners, certified nurse anesthetists, physician assistants, clinical nurse specialists, anesthesiology assistants and certified nurse midwives), and teaching hospitals and physician ownership and investment interests, including such ownership and investment interests held by a physician's immediate family members.

There are also state and foreign law equivalents of each of the above federal laws, such as state anti-kickback and false claims laws, that may impose similar or more prohibitive restrictions, and may apply to items or services reimbursed by any non-governmental third-party payors, including private insurers. Similar restrictions are also 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.

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.

***Data Privacy and Security***

Numerous state, federal and foreign laws, regulations, and standards govern the collection, use, access to, confidentiality and security of health-related and other personal information, and could apply now or in the future to our operations or the operations of our partners. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws and consumer protection laws and regulations govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, certain foreign laws govern the privacy and security of personal data, including health-related data. For example, the General Data Protection Regulation ("GDPR") imposes strict requirements for processing the personal data of individuals within EEA. Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. Further, from January 1, 2021, companies have had to comply with the GDPR and also the United Kingdom ("UK") GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, i.e., fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing

***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 ("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.

**Human Capital**

***Health, Wellness, and Safety***

As of December 31, 2021, our workforce consisted of 196 full-time employees reporting out of our two offices in the United States - Los Angeles, CA and San Francisco, CA - along with a field-based commercial team. On November 2, 2021, the Company implemented a restructuring of the organization in part due to the impact of COVID-19 on the Company's sales. The restructuring included an overall reduction in headcount of approximately 13%, consisting primarily of commercial and research personnel. We are an equal opportunity employer and believe strongly in hiring a diverse, equitable, and inclusive workforce. This is reflected in our numbers with our total workforce being approximately 58% women, 38% ethnically diverse and 79% over the age of 40. The following table summarizes our workforce by location for the years ended December 31, 2021 and December 31, 2020:

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Los Angeles | 68 | 86 |
| South San Francisco | 42 | 67 |
| Field | 86 | 114 |
| | 196 | 267 |

We believe that the safety and health of our employees and their families is essential to our business. Our culture is driven by a desire to do what is right, and we strive to support the well-being of our employees. Beginning in March 2020, we have supported our employees and government efforts to curb the COVID-19 pandemic through a multi-faceted, communication, infrastructure, and behavior modification and enforcement effort that includes:

- establishing clear and regular COVID-19 policies, safety protocols, and updates to all employees;
- strongly encouraging all office-based employees to work from home;
- implementing protocols to address actual and suspected COVID-19 cases and potential exposure; and
- prohibiting all domestic and international non-essential travel for all employees.

Our financial, medical, and mental health benefits that were already in place prior to the COVID-19 pandemic were designed to help employees through crisis, and we further expanded our offerings to create appropriate “work from home” conditions for success and wellness, to include:

- ergonomic webinars, 1x1 evaluations, and reimbursement for ergonomic equipment;
- phone and internet subsidies;
- purchasing additional IT equipment and office supplies;
- increasing communications related to our free Employee Assistance Plans, work/life assistance programs, and mental health benefits;
- professional resiliency coaching;
- subsidized subscriptions to ClassPass – access to fitness, wellness, and mindfulness classes; and
- purchasing Fitbits for all full-time employees.

***Compensation & Benefits***

We know that developing and keeping great people is a vital part of our competitive edge and essential to providing the best patient care. For this reason, we offer a robust total compensation package in an effort to attract and engage high caliber employees.

Since 2019, we have offered personalized total compensation statements to all full-time employees. These statements provide a transparent view of each employee's monetary and non-monetary benefits. Employee's total compensation represents a broad spectrum of plans and programs designed to reward and motivate employees throughout their careers.

Our total rewards package consists of competitive market-based salary and cash target bonus based on geography for every employee. Bonus opportunity and equity compensation increase as a percentage of total compensation based on level of responsibility with actual bonus payout based on performance.

In addition to competitive salaries and performance incentives, we offer employees 100% employer-paid benefits that include medical, dental, vision, life insurance, paid time off and family leave, 401(k) match, fertility benefits, volunteer days and more. Our benefit programs are constantly evolving to meet our employees' needs and renew our commitment to them as a vital resource to our continued success.

***Culture and Communication***

How we conduct our business is just as important as what we do. Our core values are the principles that guide our company strategy and our individual actions. At all times we strive to distinguish ourselves as a respected biopharmaceutical company that is differentiated by top talent and innovative products to enhance cancer care.

All employees are responsible for upholding our core values, including to be patient-centric, to communicate, collaborate, innovate and be respectful, as well as for adhering to our Code of Ethics. These values nurture an inclusive workforce striving for excellence that puts the well-being of our patients first. We continue to utilize our Human Resources Information System, or HRIS, platform to track human capital metrics, employee demographics and turnover. The majority of our employees have obtained advanced degrees in their professions, and we support their continued development with individualized development plans and objectives, mentoring, coaching, training and conference attendance.

Communication is critical in our ability to continuously enhance our company culture and create a more inclusive environment. The implementation and distribution of quarterly company newsletters have allowed us to share what is important and impactful to us as a business. It also allows for us to share stories and events that have affected our employees and co-workers across the country on both a personal and professional level. We hold town halls with our leaders to speak with employees about our vision and to receive feedback on matters important to them. Additionally, we have dynamic information technology systems, which allow for a more synergistic atmosphere.

**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, Nominating and Corporate Governance Committee Charter and Research and Development Committee Charter. We will disclose on a current report on Form 8-K or on our website 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 Puma Biotechnology, Inc., a privately-held Delaware corporation formed on September 15, 2010, or Former Puma, in October 2011. As a result of this transaction, Former Puma became 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."

## 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 and 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 Financial Condition and Capital Requirements

***We have a history of operating losses and are not profitable and may never become profitable.***

We have a history of operating losses, with net losses of approximately $29.1 million, approximately $60.0 million, and approximately $75.6 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, we had an accumulated deficit of approximately $1,366.8 million, outstanding indebtedness of approximately $97.1 million and cash and cash equivalents and marketable securities of approximately $82.1 million. We have devoted substantially all of our resources to identifying, acquiring and developing NERLYNX and to its commercialization in the indications for which it has received regulatory approval. Biopharmaceutical development is a highly speculative undertaking and involves a substantial degree of risk. We anticipate that we will continue to incur operating losses for the foreseeable future as our efforts to commercialize NERLYNX in existing indications, and develop NERLYNX for additional indications continue.

In 2017, the FDA approved NERLYNX for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy. In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. In 2018, the EC granted a marketing authorization for NERLYNX in the EU for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year from the completion of prior adjuvant trastuzumab-based therapy. Although we have begun to commercialize NERLYNX in the U.S. and Europe in these indications, we continue to experience net losses and may never become profitable. Moreover, we are continuing to develop NERLYNX for additional indications. 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;
- participating in regulatory approval processes;
- formulating and manufacturing products;
- successfully conducting sales and marketing activities; and
- implementing additional internal systems and infrastructure.

We will need to generate significant revenue in order to achieve and maintain profitability. We may not be able to generate this revenue 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.

***We are currently a single product company with limited commercial sales experience.***

We have invested a significant portion of our efforts and financial resources in the development and commercialization of our lead product, NERLYNX. NERLYNX is the only product for which we currently receive product revenue, and we expect NERLYNX to constitute the vast majority of our product revenue for the foreseeable future. By virtue of being dependent on a single product, we do not have the ability to spread out risk or commercial fluctuations across a portfolio of products. As a result, our success depends almost entirely on the commercial success of NERLYNX. NERLYNX is the first product that we, as an organization, have launched and commercialized, and there is no guarantee that we will be able to do so successfully. 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.

***We may not be able to successfully commercialize NERLYNX.***

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 or continue to take NERLYNX, due to the related side effects, including diarrhea, or otherwise, the commercial success of NERLYNX will be limited. Thus, significant uncertainty remains regarding the commercial potential of NERLYNX. We believe our ability to effectively increase product revenue from NERLYNX will depend on our ability to, among other things:

- achieve and maintain compliance with regulatory requirements;
- create and sustain 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);
- educate physicians and patients about the benefits, administration and use of NERLYNX;
- train, deploy and support a qualified sales force;
- secure formulary or pathway approvals for NERLYNX at a substantial number of accounts;
- ensure that our third-party manufacturers manufacture NERLYNX in sufficient quantities, in compliance with requirements of the FDA and similar foreign regulatory agencies where NERLYNX is approved, 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 ("cGMP") or similar foreign 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;
- 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.

We cannot assure you that we will successfully address each of these uncertainties or any others we may face in the commercialization of NERLYNX. In addition, we are dependent on international third-party sub-licensees for the development and commercialization of NERLYNX in several countries outside the United States. The failure of these sub-licensees to meet their contractual, regulatory or other obligations could adversely affect international sales of NERLYNX and hinder our ability to generate revenue. These uncertainties, combined with our limited experience in selling and marketing NERLYNX, make it difficult to evaluate our current business, predict our future prospects and forecast our financial performance.

***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. As we continue to commercialize NERLYNX, our costs and expenses may increase in the future due to, among other things, 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. We are party to a Note Purchase Agreement with Athyrium, providing for potential issuance of notes of up to $125.0 million, which mature on July 23, 2026. As of December 31, 2021, we had $100.0 million in principal amounts outstanding. 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, our success in commercializing neratinib, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time.

***The terms of our Note Purchase Agreement 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 Note Purchase Agreement or to satisfy the minimum revenue and cash balance covenants.***

The terms of our Note Purchase Agreement place restrictions on our ability to operate our business and on our financial flexibility. As of December 31, 2021, the aggregate principal amount outstanding under the notes sold pursuant to the Note Purchase Agreement (collectively, the "Notes") was $100.0 million. The Notes are secured by collateral which consists of our equity interests in our domestic and foreign subsidiaries (including up to 100% of the issued and outstanding equity interests in each of our domestic subsidiaries directly owned by us or the guarantors of the Notes) and substantially all of our property, other than our intellectual property. In addition to voluntary prepayments, we may also be required to make mandatory prepayments under the Notes in varying amounts within three (3) business days of the occurrence of certain events, including in the event that we receive proceeds from a voluntary or involuntary disposition and such proceeds are not reinvested in eligible assets within 180 days of the date of such disposition, or in the event that we receive extraordinary receipt cash proceeds and such proceeds are not reinvested in eligible assets within 180 days of the date of such extraordinary receipt. The Note Purchase Agreement includes affirmative and negative covenants applicable to us and our subsidiaries. The affirmative covenants include, but are not limited to, requirements to (i) maintain our legal existence and take all reasonable actions to maintain our rights, privileges and authorizations (including renewal of permits or licenses) necessary to conduct our business and maintain our intellectual property, (ii) deliver certain financial statements, certificates and other information to Athyrium on a regular basis, (iii) maintain adequate insurance coverage with respect to the properties and business and (iv) cause all of our deposit accounts to be subject to Deposit Account Control Agreements. The negative covenants include, but are not limited to, restrictions on (i) creating or incurring certain liens on our property, assets or revenues, (ii) making certain investments or incurring additional indebtedness, (iii) engaging in certain business or strategic activities (including transactions with affiliates or insiders) and (iv) paying certain dividends, distributions or other restricted payments. Additionally, pursuant to the Note Purchase Agreement, we must maintain a minimum cash balance in our accounts subject to a Deposit Account Control Agreement and must achieve certain levels of product revenue for any four (4) consecutive fiscal quarter periods. These affirmative and negative 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 product revenue requirements or minimum cash balance requirements under the Note Purchase Agreement. Our failure to satisfy such requirements, or our direct or indirect breach of certain other covenants, could result in an event of default under the Notes. The occurrence and continuation of an event of default could (i) cause interest to accrue at a rate per annum equal to the applicable interest rate under the Note Purchase Agreement *plus* two percent (2.00%) and (ii) cause accrued and unpaid interest on past due amounts (including interest thereon) to be due and payable in cash on demand. Additionally, upon the occurrence or continuation of an event of default, Athyrium, in its capacity as administrative agent, would have the right to exercise remedies against us, including declaring the unpaid principal amount under the Note (and interest thereon) immediately due and payable, and foreclosure against the property securing the Notes (including our cash). Other events of default under the Note Purchase Agreement include, but are not limited to, (i) our failure to pay principal or interest due under the Note Purchase Agreement, (ii) our insolvency or related actions (including an assignment for the benefit of creditors), (iii) the existence of material adverse changes in our business or products, (iv) the occurrence of any default under certain other indebtedness in an amount greater than $750,000 or one or more judgments against us in an amount greater than $750,000 individually or in the aggregate that remains unsatisfied, unvacated or unstayed for a period of ten (10) days after its entry and (v) the delisting of our shares of common stock from the Nasdaq Capital Market.

**Risks Related to Commercialization of our Product Candidates**

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

A key part of our strategy is to continue to build our sales, marketing and distribution capabilities to commercialize NERLYNX successfully in the United States. In order to market NERLYNX successfully, 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 and maintain adequate sales, marketing, and distribution capabilities, whether independently or with third parties, we may not be able to commercialize NERLYNX appropriately and may not become profitable.

In the United States, we rely on a direct sales force. NERLYNX is a marketed drug and none of the members of our sales force had ever promoted NERLYNX prior to its commercial launch. There are risks with establishing, growing and maintaining our own sales and marketing capabilities, 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 need to train our sales force to ensure that a consistent and appropriate message about NERLYNX is being delivered to our potential customers;
- the inability of sales personnel to obtain access to physicians or convince adequate numbers of physicians to prescribe any product;
- our inability to equip the sales force with effective materials, including medical and sales literature, to help them inform and educate physicians and patients about the benefits of NERLYNX and its proper administration;
- 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.

If we are unable to effectively address these risks, our efforts to commercialize NERLYNX successfully 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.

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 depend on a limited number of customers for a significant amount of our total revenue, and if we lose any of our significant customers, our business could be harmed.***

The majority of our revenue comes from a limited number of customers. In 2021, two customers individually comprised approximately 31% and 22%, respectively, of our total product revenue. We expect that revenue from a limited number of customers will continue to account for a large portion of our revenue in the future. The loss by us of any of these customers, or a material reduction in their purchases or their market pricing, could harm our business, results of operations, financial condition and prospects. In addition, if any of these customers were to fail to pay us in a timely manner, it could harm our cash flow.

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

Even though the FDA and EC have granted approval of NERLYNX, the scope and terms of the approvals may limit our ability to commercialize NERLYNX and, therefore, our ability to generate substantial sales revenue. The FDA and EC have both approved NERLYNX for the extended adjuvant treatment of early stage, HER2-positive breast cancer in patients who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. In connection with the FDA and EC approvals, we have committed to conduct certain post-marketing studies. We have completed the post-marketing commitments related to the FDA approval, and the post-marketing studies related to the EC approval are ongoing. If we fail to comply with all of 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 or the EC could decide to withdraw its respective approval, add warnings or narrow the approved indication in the product label.

***Regulatory approval for any approved product is limited by the FDA and foreign regulatory authorities 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 and foreign regulatory authorities 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 or foreign regulatory authorities grant is limited to those specific diseases and indications for which a product is deemed to be safe and effective by the FDA and foreign regulatory authorities. 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, and in combination with capecitabine, to the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. In addition to the FDA or foreign regulatory authorities approval required for new formulations, any new indication for an approved product also requires FDA or foreign regulatory authorities 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 and abroad 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 or foreign regulatory authorities. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. For example, in April 2018, we announced that NERLYNX (neratinib) has been included as a recommended treatment option in the latest NCCN Clinical Practice Guidelines in Oncology Central Nervous System Cancers for Breast Cancer patients with brain metastases. The NCCN designated NERLYNX in combination with capecitabine as a category 2A treatment option and NERLYNX in combination with paclitaxel as a category 2B treatment option. Use, as designated for breast cancer patients with brain metastases, is outside the FDA approved indication for NERLYNX and considered investigational, and we do not market or promote NERLYNX for these uses. Regulatory authorities in the United States and abroad 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 or foreign regulatory authorities' regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to

follow FDA or foreign regulatory authorities rules and guidelines relating to promotion and advertising may cause the FDA or foreign regulatory authorities 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.

***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 and not generally distributed through the retail channel;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 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, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an Executive Order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The Executive Order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work

requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the 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 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 2030, with the exception of a temporary suspension from May 1, 2020 through July 1, 2022 (with a 1% payment reduction from April 1 to June 30, 2022), 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.

The cost of prescription pharmaceuticals in the United States has also been the subject of considerable discussion. There have been several Congressional inquiries, as well as legislative and regulatory initiatives and executive orders 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. Members of Congress and the Biden Administration have indicated they will continue to pursue legislative or administrative measures to control prescription drug costs, although the likelihood of such measures being adopted remains uncertain. For example, the Build Back Better Act, if enacted, would introduce substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, and the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D. If the Build Back Better Act is not enacted, similar or other drug pricing proposals could appear in future legislation. We cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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 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.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize NERLYNX and our other product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national

regulatory burdens on those wishing to develop and market products, this could restrict or regulate post-approval activities and affect our ability to commercialize NERLYNX and our other product candidates, if approved. In other international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, NERLYNX may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

***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 our current or future commercial products, 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 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 to federal, state and foreign healthcare fraud and abuse laws, false claims laws and physician payment transparency 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, state and foreign healthcare laws and regulations pertaining to fraud and abuse and physician payment transparency laws and regulations 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.;

- 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. 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;

- 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 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), certain non-physician practitioners (nurse practitioners, certified nurse anesthetists, physician assistants, clinical nurse specialists, anesthesiology assistants and certified nurse midwives), 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 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; and 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

- European and other foreign law equivalents of each of these laws, including reporting requirements detailing interactions with and payments to healthcare providers.

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 or foreign regulatory authority requirements, including those laws that require the reporting of true, complete and accurate information to the FDA or foreign regulatory authorities, 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 ("MDRP") 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. As a condition of having federal funds being made available for our covered outpatient drugs under Medicaid and Medicare Part B, we have enrolled in the MDRP, which requires us to pay a rebate to state Medicaid programs for each unit of our covered outpatient drugs dispensed to a Medicaid beneficiary and paid for by a state Medicaid program. Medicaid drug rebates are based on pricing data that we must report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price ("AMP") for each drug and, in the case of our innovator products, the best price ("BP"). If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. In addition, there is increased focus by the Office of Inspector General within the U.S. Department of Health and Human Services on the methodologies used by manufacturers to calculate AMP, and BP, to assess manufacturer compliance with MDRP reporting requirements. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP, which would result in payment not being available for our covered outpatient drugs under Medicaid or, if applicable, Medicare Part B. 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.

Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. We participate in the 340B program, which is administered by the Health Resources and Services Administration ("HRSA"), and requires us to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered outpatient drugs used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B-eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and Medicare Part B and purchased by certain federal agencies and grantees, we also must participate in the U.S. Department of Veterans Affairs ("VA") Federal Supply Schedule ("FSS") pricing program. Under the VA/FSS program, we must report the Non-Federal Average Manufacturer Price ("Non-FAMP") for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non-FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). We must also pay rebates on products purchased by military personnel and dependents through the

TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information. If we are found to have violated state law requirements, we may become subject to penalties or other enforcement mechanisms, which could have a material adverse effect on our business.

Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. The terms, scope and complexity of these government pricing programs change frequently, as do interpretations of applicable requirements for pricing and rebate calculations. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming. 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. Price recalculations under the MDRP also may affect the ceiling price at which we are required to offer products under the 340B program. Civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. In the event that CMS were to terminate our Medicaid rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs. We cannot assure you that our submissions will not be found to be incomplete or incorrect.

**Risks Related to the Discovery and Development of our Products**

***Interim, "topline" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.***

From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Preliminary and topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. Consequently, preliminary and topline data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our clinical trial. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

In addition, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure.

If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

***NERLYNX or our other drug candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs 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, including in combination with other approved products or investigational new drugs, 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.

***NERLYNX is still under clinical development for various additional indications, and we cannot be certain that NERLYNX will receive regulatory approval for any other indication for which we may seek approval.***

The FDA and the EC have both approved NERLYNX for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. In February 2020, the FDA also approved NERLYNX in combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. 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 or in the EU until we receive approval from the EC, as applicable, for such indications, or, in any foreign countries, until requisite approval from such countries.

Approval of NERLYNX by the FDA or the EC for any particular indication does not ensure that a foreign jurisdiction will also approve NERLYNX for such indication, nor does it ensure that NERLYNX will be approved by the FDA or the EC 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 regulators may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the 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 or other regulator may require development of a Risk Evaluation and Mitigation Strategy or similar risk management measures 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, whether in the United States or in other jurisdictions, we will not be able to market NERLYNX for such indications in those jurisdictions, which will limit our commercial revenue.

***We are subject to ongoing obligations and continued regulatory review with regard to NERLYNX and any other drug candidates that may receive FDA or foreign regulatory approval, which may result in significant 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 similar requirements 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 or foreign regulatory authorities 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 and foreign regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our drug candidates. 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. 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 be subject to enforcement action, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

***Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business.***

The ability of the FDA and foreign regulatory authorities to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's and foreign regulatory authorities' ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's and foreign regulatory authorities' ability to perform routine functions. Average review times at the FDA and foreign regulatory authorities have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies, such as the European Medicines Agency ("EMA") following its relocation to Amsterdam and resulting staff changes, may also slow the time necessary for new drugs or modifications to approved drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to the COVID-19 pandemic, in March 2020 the FDA announced its intention to postpone most inspections of foreign manufacturing facilities, and on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, in July 2020 the FDA resumed certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA utilized this risk-based assessment system to assist in determining when and where it was safest to conduct prioritized domestic inspections. Additionally, on April 15, 2021, the FDA issued a guidance document in which the FDA described its plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites, among other facilities. According to the guidance, the FDA may request such remote interactive evaluations where the FDA determines that remote evaluation would be appropriate based on mission needs and travel limitations. In May 2021, the FDA outlined a detailed plan to move toward a more consistent state of inspectional operations, and in July 2021, the FDA resumed standard inspectional operations of domestic facilities and was continuing to maintain this level of operation as of September 2021. More recently, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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

Although NERLYNX has been approved by the FDA for the extended adjuvant treatment of early stage, HER2-positive breast cancer, and in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting, and by the EC for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago, NERLYNX is still under development for various indications in the United States and in the EU, and our other drug candidates are in development, as well, all of which will require extensive clinical testing before we can submit any NDA or similar foreign entities for regulatory approval. We cannot predict with any certainty that any NDA or supplemental NDA (or similar foreign applications) seeking to expand the indication for NERLYNX will be approved by the FDA or foreign regulatory authorities. 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.

We do not know whether our future clinical trials will begin on time or enroll patients on time, or whether our ongoing and/or future clinical trials will be completed on schedule or at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical studies;
- obtaining regulatory authorizations to commence a trial or reaching a consensus with regulatory authorities on trial design;
- any failure or delay in reaching an agreement with CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining approval from one or more institutional review boards, or IRBs or ethics committees;
- IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing their approval of the trial;
- changes to clinical trial protocol;
- clinical sites deviating from trial protocol or dropping out of a trial;
- manufacturing sufficient quantities of product candidate or obtaining sufficient quantities of combination therapies for use in clinical trials;
- subjects failing to enroll or remain in our trial at the rate we expect, or failing to return for post- treatment follow-up;
- subjects choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trial;
- subjects experiencing severe or unexpected drug-related adverse effects;
- occurrence of serious adverse events in trials of the same class of agents conducted by other companies;
- selection of clinical end points that require prolonged periods of clinical observation or analysis of the resulting data;

- a facility manufacturing our product candidates or any of their components being ordered by the FDA or comparable foreign regulatory authorities to temporarily or permanently shut down due to violations of current good manufacturing practice, or cGMP, regulations or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, good clinical practices, or GCP, or other regulatory requirements;
- third-party contractors not performing data collection or analysis in a timely or accurate manner; or
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. Further, we, the FDA, foreign regulatory authorities, or an 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.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The EU CTR which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate CTA to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials whose CTA was made under the Clinical Trials Directive before January 31, 2022, the Clinical Trials Directive will continue to apply on a transitional basis for three years. Additionally, sponsors may still choose to submit a CTA under either the Clinical Trials Directive or the CTR until January 31, 2023 and, if authorized, those will be governed by the Clinical Trials Directive until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR.

If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted.

***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.

Moreover, pre-clinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or comparable foreign regulatory authority approval. We cannot guarantee that the FDA or foreign regulatory authorities will interpret trial results as we do, and more trials could be required before we are able to submit applications seeking approval of our product candidates. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates. Even if regulatory approval is secured for any of our product candidates, the terms of such approval may limit the scope and use of our product candidate, which may also limit its commercial potential. Furthermore, the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval, which may lead to the FDA or comparable foreign regulatory authorities delaying, limiting or denying approval of our product candidates.

**Risks Related to Third Parties**

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

We have entered into exclusive sub-license agreements with several third parties that provide these sub-licensees exclusive rights to the development and commercialization of NERLYNX in Europe (excluding Russia and Ukraine), Australia, Canada, China, Southeast Asia, Israel, South Korea, and various countries and territories in Central and South America. 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 in those regions outside of the United States, 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 to 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; 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 to 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.

Any termination, breach or expiration of any of these sub-license agreements could have a material adverse effect on our financial position by reducing or eliminating the potential for us to receive license fees, milestones and royalties. In such an event, we may be required to devote additional efforts and to incur additional costs associated with pursuing regulatory approval and commercialization of the applicable products and product candidates. Alternatively, we may attempt to identify and transact with a new sub-licensee, but there can be no assurance that we would be able to identify a suitable sub-licensee or transact on terms that are favorable to us.

***We have no experience in drug formulation or manufacturing and 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 or foreign regulatory authorities 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 or foreign regulatory authorities pursuant to inspections that are conducted following submission of an NDA to the FDA or pursuant to similar foreign applications to foreign regulatory authorities. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMP or similar foreign 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 and 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 or similar foreign 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 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 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 or similar foreign 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 or foreign 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.

**Risks Related to our Business Operations**

***Our business, financial condition, results of operations and ongoing clinical trials have been and could continue to be harmed by the effects of the COVID-19 pandemic.***

We are subject to various risks related to the global pandemic associated with COVID-19. For example, many geographic regions have imposed, or in the future may impose, "shelter-in-place" orders, quarantines or similar orders or restrictions to control the spread of COVID-19. These types of restrictions have deterred and may continue to deter or prevent cancer patients from traveling to see their doctors and result in a decline in new patient enrollments/new patient starts and in revenue for NERLYNX, our only commercial product. Additionally, our commercial team, field medical and sales force have been forced to suspend the majority of their travel and personal interactions with physicians and customers,

including visits to healthcare provider offices or clinics. The commercial team and sales force are currently limited to conducting the majority of their promotional activities virtually. The respective commercial teams of certain of the companies to which we sub-license the commercial rights of NERLYNX, and on which we rely for our international sales, have chosen or have been forced to take similar action, and other sub-licensees of NERLYNX may choose or be forced to take similar action. Furthermore, the pandemic has resulted in dramatic increases in unemployment rates, which resulted in a number of people becoming uninsured or underinsured, and this trend may continue. These developments have had and may continue to have an adverse effect on our revenue and thus could have an adverse effect on our ability to satisfy the minimum revenue and cash balance covenants in our loan and security agreement.

Moreover, these types of restrictions have resulted in most of our other employees working from home and the employees of our key third-party vendors and manufacturers working from home. We rely exclusively on third-party manufacturers to manufacture NERLYNX. Neither we, nor our suppliers or manufacturers have significant experience operating with the majority of our respective work forces working from home, and this has disrupted and may continue to disrupt standard operations for us or them, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our respective abilities to conduct business in the ordinary course. In addition, this may increase our cybersecurity risk, create data accessibility concerns and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with local and federal regulators, ethics committees, manufacturing sites, research or clinical trial sites and other important agencies and contractors. Our business interruption insurance, if available at all, may be insufficient to cover losses resulting from extended business interruptions from the COVID-19 pandemic.

Additionally, timely enrollment in our clinical trials is dependent upon global clinical trial sites, which have been and may continue to be adversely affected by the COVID-19 pandemic. We are currently conducting clinical trials for our product candidates in many countries, including the United States, the United Kingdom, Spain, Italy, France, South Korea, Australia, and Israel, and may expand to other geographies. Many of these regions have been and may continue to be affected by the COVID-19 pandemic. We have observed disruptions in patient enrollments in the United States and our SUMMIT basket trial. If the COVID-19 pandemic continues to spread in the geographies in which we are conducting clinical trials, we may continue to experience additional disruptions in those clinical trials, which could have a material adverse impact on our clinical trial plans and timelines, including:

- delays in receiving authorizations from local regulatory authorities and ethics committees to initiate planned clinical trials;
- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruptions in global shipping that may affect the transport of clinical trial materials;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;
- risk that participants enrolled in our clinical trials will contract COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- delays in necessary interactions with local regulators, ethics committees and other third parties and contractors due to limitations in employee resources or forced furlough of government employees;
- limitations in employee resources that would otherwise be focused on the conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people; and
- refusal of the FDA or foreign regulatory authorities to accept data from clinical trials in affected geographies.

The continued spread of COVID-19 has also led to extreme disruption and volatility in the global capital markets, which increases the cost of, and adversely impacts access to, capital and increases economic uncertainty. While COVID-19 has had an adverse impact on our business and may continue to do so, given the rapid and evolving nature of the virus and the uncertainty about its impact on society and the global economy, we cannot predict the extent to which it will affect our global operations, particularly if these impacts persist or worsen over an extended period of time. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also affect our ability to comply with certain covenants in our loan and security agreement or other agreements that are material to our business.

***Engaging in international business subjects us to additional business and regulatory risks, and there can be no assurance that our products will be accepted in those markets.***

We have entered into exclusive sub-license agreements providing for third parties to pursue regulatory approval and commercialize NERLYNX, if approved, in various specified regions outside of the United States. We plan to continue to pursue commercialization of NERLYNX in additional countries outside the United States where it has been 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 sub-licensees or 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, 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.

***We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm us.***

Our internal computer systems and those of third parties with which we contract may be vulnerable to damage from cyber-attacks, "phishing" attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures despite the implementation of security measures. Attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. As a result of the COVID-19 pandemic, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. 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.

***Compliance with governmental regulation and other legal obligations related to privacy, data protection and information security could result in additional costs and liabilities to us or inhibit our ability to collect and process data, and the failure to comply with such requirements could have a material adverse effect on our business, financial condition or results of operations.***

Privacy and data security have become significant issues in the United States, Europe and in many other jurisdictions where we may in the future conduct our operations. As we receive, collect, process, use and store personal and confidential data, we are subject to diverse laws and regulations relating to data privacy and security. In the United States, numerous federal and state laws and regulations could apply to our operations or the operations of our partners, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws and regulations (e.g. Section 5 of the FTC Act), that govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Depending on

the facts and circumstances, we could be subject to criminal penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

Further, certain states have also enacted data privacy and security laws. For example, the California Consumer Privacy Act ("CCPA") went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability, and similar laws have been proposed at the federal level and in other states. Further, the California Privacy Rights Act ("CPRA") recently passed in California. The CPRA significantly amends the CCPA and will impose additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It will also create a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. The majority of the provisions will go into effect on January 1, 2023, and additional compliance investment and potential business process changes may be required. Similar laws have passed in Virginia and Colorado, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. Compliance with these privacy and data security requirements is rigorous and time-intensive and may increase our cost of doing business; despite those efforts, there is a risk that we may be subject to fines and penalties, litigation and reputational harm, which could materially and adversely affect our business, financial condition and results of operations.

Furthermore, the FTC, and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive. For example, according to the FTC, failing to take appropriate steps to keep consumers' personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act. The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities.

In addition, the regulatory framework for the receipt, collection, processing, use, safeguarding, sharing and transfer of personal and confidential data is rapidly evolving and is likely to remain uncertain for the foreseeable future as new global privacy rules are being enacted and existing ones are being updated and strengthened. For example, on May 25, 2018, the GDPR took effect in Europe. The GDPR is directly applicable in each European Union and EEA member state and applies to companies established in the European Union and the EEA as well as companies that collect and use personal data to offer goods or services to, or monitor the behavior of, individuals in the European Union and the EEA. GDPR imposes stringent data protection obligations for processors and controllers of personal data, and penalties and fines for failure to comply with GDPR are significant, including fines of up to €20 million or 4% of total worldwide annual turnover, whichever is higher. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the EU ("CJEU"), limited how organizations could lawfully transfer personal data from the EU/EEA to the United States by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses (SCCs). The European Commission issued revised SCCs on June 4, 2021 to account for the decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. The new SCCs apply only to the transfer of personal data outside of the EEA and not the UK; the UK's Information Commissioner's Office launched a public consultation on its draft revised data transfers mechanisms in August 2021. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers to non-EEA entities subject to the GDPR. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results

Further, since January 1, 2021, companies have to comply with the GDPR and also the UK GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, i.e., fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term. The European Commission has adopted an adequacy decision in favor of the United Kingdom, enabling data transfers from EU member states to the United Kingdom without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the European Commission re-assesses and renews or extends that decision.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, collaborators, or other third parties to comply with such requirements or adequately address privacy and security concerns, even if unfounded, could result in additional cost and liability to us, damage our reputation, and adversely affect our business and results of operations.

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

The market for our 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 or foreign regulatory 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 depend, 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, 2021, we had 196 employees. 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 and product recalls.***

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.

Product recalls may be issued at our discretion, or at the discretion of government agencies and other entities that have regulatory authority for pharmaceutical sales. Any recall of NERLYNX could materially adversely affect our business by rendering us unable to sell NERLYNX for some time and by adversely affecting our reputation.

***We may in the future engage in strategic transactions that increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.***

We actively evaluate various strategic transactions on an ongoing basis, including licensing or otherwise acquiring complementary products, technologies or businesses. Any potential future acquisitions or in-licensing transactions entail numerous risks, including but not limited to:

- risks associated with satisfying the closing conditions relating to such transactions and realizing their anticipated benefits;
- increased operating expenses and cash requirements;
- difficulty integrating acquired technologies, products, operations, and personnel with our existing business;
- the potential disruption of our historical core business;
- diversion of management's attention in connection with both negotiating the acquisition or license and integrating the business, technology or product;
- retention of key employees;
- difficulties in assimilating employees and corporate cultures of any acquired companies;
- uncertainties in our ability to maintain key business relationships of any acquired companies;
- strain on managerial and operational resources;
- difficulty implementing and maintaining effective internal control over financial reporting at businesses that we acquire, particularly if they are not located near our existing operations;
- exposure to unanticipated liabilities of acquired companies or companies in which we invest;
- the potential need to write down assets or recognize impairment charges; and
- potential costly and time-consuming litigation, including stockholder lawsuits.

As a result of these or other problems and risks, businesses, technologies or products we acquire or invest in or obtain licenses to may not produce the revenues, earnings or business synergies that we anticipated, acquired or licensed product candidates or technologies may not result in regulatory approvals, and acquired or licensed products may not perform as expected. As a result, we may incur higher costs and realize lower revenues than we had anticipated. We cannot assure you that any acquisitions or investments we have made or may make in the future will be completed or that, if completed, the acquired business, licenses, investments, products, or technologies will generate sufficient revenue to offset the negative costs or other negative effects on our business. Failure to effectively manage our growth through acquisition or in-licensing transactions could adversely affect our growth prospects, business, results of operations, financial condition, and cash flow.

In addition, we may spend significant amounts, issue dilutive securities, assume or incur significant debt obligations, incur large one-time expenses and acquire intangible assets or goodwill in connection with acquisitions and in-licensing transactions that could result in significant future amortization expense and write-offs. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business. Other pharmaceutical companies, many of which may have substantially greater financial, marketing and sales resources, compete with us for these opportunities. Even if appropriate opportunities are available, we may not be able to successfully identify them or we may not have the financial resources necessary to pursue them, and if pursued, we may be unable to structure and execute transactions in the anticipated timeframe, or at all.

**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 and regulatory exclusivity periods 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 (if any are allowed at all) 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, and the outcome of which is unpredictable.

The patents we have licensed may be challenged and could be invalidated or rendered unenforceable by third parties. There is no guarantee that a court would agree that any of the patents we have licensed, and which are currently in force, are valid or enforceable. Challenges to the breadth or strength of protection provided by any patents we have licensed, or patent applications we may pursue in the future, with respect to any of our current or future product candidates or products, could threaten our ability to commercialize any of our current or future product candidates or products. 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.

The patents we have licensed may be affected by certain provisions of the America Invents Act, or AIA, enacted in 2011. For example, under the AIA, members of the public may seek to challenge an issued patent by petitioning the USPTO to institute a post grant proceeding, such as a Post Grant Review, or PGR, or Inter Parties Review, or IPR. Once a post grant proceeding is instituted, the USPTO may find grounds to revoke the challenged patent or specific claims therein. A similar procedure (known as a patent opposition) has existed in Europe for many years and we have defended, and continue to defend, our European patents in certain of those proceedings. We cannot predict whether any other licensed patents will become the subject of a post grant proceeding or patent opposition. If a significant product patent is successfully challenged in a post grant proceeding or patent opposition, it may be revoked, which would have a serious negative impact on our ability to maintain exclusivity in the market-place for our commercial products affected by such revocation and could adversely affect our future revenues and profitability.

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. Such disclosure could adversely affect our ability to prevent further disclosures of our trade secrets. 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 be enforceable, 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.

Following the expiration of patents and any regulatory exclusivity we are able to obtain, we expect competitors may manufacture and sell generic versions of our products, at a lower price, which would reduce revenues obtained from such products. Notably, legislation in some jurisdictions mandates generic substitution for brand name drugs.

***We may not be able to protect our intellectual property rights throughout the world.***

Filing, prosecuting, and defending our intellectual property rights in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. For instance, some jurisdictions, such as China and India, do not consider methods of treating the human body as patentable. Further, licensing partners may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products, and our intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our intellectual property rights or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our proprietary rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our proprietary rights at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Certain fees, including maintenance, renewal, annuity, and other governmental fees, on patents and/or applications are periodically due to be paid to the USPTO and various foreign governmental patent agencies at certain stages over the lifetime of the patents and/or applications. We have systems in place and employ third-party firms to monitor due dates and pay these fees. We also employ law firms and other reputable professionals to assist us in the event an inadvertent lapse can be cured by payment of a late fee or by other means according to the applicable jurisdictional laws and rules. Non-compliance, in certain circumstances, can result in abandonment or lapse of the patent (or patent application) and result in a partial or even complete loss of patent rights in the particular jurisdiction. Our competitors might be able to enter the market under such circumstances, resulting in a possible 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 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. Holders of such intellectual property rights are not required to give us a license if one were required. 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 inter partes review or post-grant review petitions in the USPTO to invalidate our issued U.S. patents, we may have to participate in such proceedings to defend such patents. 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. The outcome of such proceedings in the United States and foreign countries is predictable. Some of our competitors may be able to sustain the costs of such proceedings and 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 such proceedings or 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, using, selling, offering for sale, importing 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**

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

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

- the level of sales of NERLYNX;
- the overall demand for NERLYNX, including the customer ordering and discontinuation patterns
- 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;
- developments involving our sublicensees;
- 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 developments in, litigation involving us;
- market conditions in the biopharmaceutical industry;
- timing and announcement of regulatory approvals;
- changes in government regulation that affect us or the biopharmaceutical industry more generally;
- 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.

***We have been subject to securities litigation in the past, and volatility in the price of our common stock may subject us to securities litigation in the future.***

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. These types of lawsuits are subject to inherent uncertainties, and are expensive and time-consuming to investigate, defend and resolve. For instance, in Hsu v. Puma Biotechnology, Inc., the plaintiff alleged 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 the Exchange Act. In February 2019, a jury found that three of the four challenged statements were not false and misleading, and thus found in the defendants' favor on those claims. In December 2021, the Court issued an order preliminarily approving the parties' settlement which provides for payment by us of approximately $54.2 million in two installments to be paid in January and June of 2022. Any other litigation to which we are a party may similarly divert our management's attention and financial and other resources, or result in an onerous or unfavorable judgment that may not be reversed upon appeal or in payments of substantial monetary damages or fines. Additionally, we may decide to settle such lawsuits on similarly unfavorable terms, which could adversely affect our business, financial condition, results of operations or stock price.

***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. In November 2021, we also entered into an Open Market Sales Agreement[SM] with Jefferies LLC pursuant to which we may offer and sell shares of common stock having an aggregate offering price of up to $50.0 million from time to time, in any method that is deemed to be an "at the market" offering as defined in Rule 415(a)(4) of the Securities Act. 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.***

Our founder, Chief Executive Officer and President, Alan H. Auerbach, holds a warrant 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 prior to its expiration in October 2026, our stockholders may experience immediate dilution and the market price of our common stock may be adversely affected.

***We incur increased costs and demands upon management as a result of complying with the laws and regulations affecting public companies.***

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. These rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

These rules and regulations may also 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.

***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 Note Purchase Agreement with Athyrium. 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 65,656 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 February 2019, we entered into a long-term sublease agreement whereby we sublease 12,429 square feet of this office space to a third party subtenant. The rental amounts payable to us pursuant to the sublease increase approximately 3% each year. The lease and the related sublease both terminate in March 2026. We also lease approximately 29,470 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. 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 v. Puma Biotechnology, Inc., et. al.***

On June 3, 2015, Hsingching Hsu, individually and on behalf of all others similarly situated, filed a class action lawsuit against us and certain of our executive officers in the United States District Court for the Central District of California (Case No. 8:15-cv-00865-AG-JCG). On October 16, 2015, lead plaintiff Norfolk Pension Fund filed a consolidated complaint on behalf of all persons who purchased our securities between July 22, 2014 and May 29, 2015. A trial on the claims relating to four statements alleged to have been false or misleading was held from January 15 to January 29, 2019. At trial, the jury found that three of the four challenged statements were not false or misleading, and thus found in the defendants' favor on those claims. On October 29, 2021, the parties informed the Court that they had reached a settlement in principle. The parties' settlement provides that there will be no judgment for liability entered against the defendants, and provided payment by us of approximately $54.2 million in two installments, to be paid in January and June of 2022. On December 13, 2021, lead plaintiff filed a motion for preliminary approval of the settlement, and on December 29, 2021, the Court issued an order preliminarily approving the settlement. The Court also set a date for the final settlement hearing, which is scheduled to be held April 11, 2022.

***Eshelman v. Puma Biotechnology, Inc., et. al.***

In February 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 alleged that we and Mr. Auerbach made defamatory statements regarding Dr. Eshelman in connection with a proxy contest. In May 2016, Dr. Eshelman filed a notice of voluntary dismissal of the claims against Mr. Auerbach. A trial on the remaining defamation claims against us took place from March 11 to March 15, 2019. At trial, the jury found us liable and awarded Dr. Eshelman $15.9 million in compensatory damages and $6.5 million in punitive damages. We strongly disagreed with the verdict and, on April 22, 2019, filed a motion for a new trial or, in the alternative, a reduced damages award. The Court denied that motion on March 2, 2020. We appealed that ruling, and the verdict. Additionally, after trial, the plaintiff filed a motion seeking approximately $3.0 million in attorneys' fees, as well as prejudgment interest. In the Court's March 2020 ruling, it denied the motion for attorneys' fees but granted the request for prejudgment interest, bringing the total judgment to $26.3 million. On March 30, 2020, the plaintiff filed a notice of cross-appeal and conditional cross-appeal, appealing the Court's order denying the plaintiff's request for attorneys' fees and conditionally cross-appealing a Court ruling that certain communications between Mr. Auerbach and his attorneys were protected by attorney-client privilege and a related evidentiary ruling. On June 23, 2021, the United States Court of Appeals for the Fourth Circuit affirmed the liability verdict in the Eshelman v. Puma Biotechnology, et. al matter but found the $22.4 million damages award, payable by us, to be excessive in light of the evidence at trial. The court vacated this award and remanded for a new trial on damages. The Court's judgment will eliminate the damages award, including interest on the judgment, pending further proceedings on remand. On July 7, 2021, the plaintiff filed a petition for panel or en banc rehearing, which was denied on July 20, 2021. On July 26, 2021, the plaintiff filed a motion to stay issuance of the Fourth Circuit's mandate pending the filing and resolution of a petition for certiorari in the Supreme Court. The Fourth Circuit denied that motion on July 29, 2021. On October 18, 2021, the plaintiff filed a petition of certiorari with the Supreme Court seeking review of the Fourth Circuit's ruling. On December 13, 2021, the Supreme Court denied plaintiff's petition for certiorari. The case remains pending in the district court, which has not yet scheduled the new trial on damages.

***CANbridge Licensing Dispute***

On July 28, 2020, we filed a request for arbitration against CANbridge Biomed Limited ("CANbridge") before the ICC International Court of Arbitration. We asserted that CANbridge violated the terms of our agreement with CANbridge in which we granted CANbridge an exclusive sublicense to develop and commercialize NERLYNX throughout greater China. We sought an arbitral award, as well as damages, costs, and attorneys' fees. On August 26, 2020, CANbridge filed its response to our request for arbitration and brought counterclaims, seeking damages, costs and attorneys' fees. On February 24, 2021, we and CANbridge resolved our dispute, with each side agreeing to dismiss our respective claims in the arbitration. The settlement is limited to claims asserted in the arbitration, or that are related to the claims asserted in the arbitration.

***Legal Malpractice Suits***

On September 17, 2020, we filed a lawsuit against Hedrick Gardner Kincheloe & Garofalo, L.L.P. and David L. Levy, the attorneys who previously represented us in Eshelman v. Puma Biotechnology, Inc., et al. in the Superior Court of Mecklenburg County, North Carolina. We are alleging legal malpractice based on the defendants' negligent handling of the defense of us in Eshelman v. Puma Biotechnology, Inc., et al. as detailed above. We are seeking recovery of the entire amount awarded in Eshelman v. Puma Biotechnology, Inc., et al. On November 23, 2020, the defendant filed an answer to the complaint denying the allegations of negligence.

On June 23, 2021, the United States Court of Appeals for the Fourth Circuit set aside the damages award in the Eshelman v. Puma Biotechnology, Inc., et al matter and remanded the case to the District Court for a new trial on damages. On October 7, 2021, Judge R. Stuart Albright entered into an Order staying all proceedings in the legal malpractice case for six months to allow time to resolve the damages issues in the Eshelman case. As a result, the amount of potential damages that may be recovered in the legal malpractice case is uncertain at this time.

***Patent-Related Proceedings***

*AstraZeneca Litigation*

On September 22, 2021, Puma filed suit against AstraZeneca Pharmaceuticals, LP, AstaZeneca AB, and AstraZeneca PLC for infringement of United States Patent Nos. 10,603,314 ("the '314 patent") and 10,596,162 ("the '162 patent"). (*Puma Biotechnology, Inc. et al. v. AstraZeneca Pharmaceuticals LP et al*, 1:21CV01338 (D. Del. Sep. 22, 2021)). Puma's complaint alleges that AstraZeneca's commercial manufacture, use, offer for sale, sale, distribution, and/or importation of Tagrisso® (osimertinib) products for the treatment of gefitinib and/or erlotinib-resistant non-small cell lung cancer infringes the '314 and '162 patents. Puma is an exclusive licensee of the '314 and '162 patents under the Pfizer Agreement. Wyeth is a co-plaintiff. Plaintiffs seek a judgment that AstraZeneca's product infringes the asserted patents and an award of monetary damages in an amount to be proven at trial. AstraZeneca AB and AstraZeneca Pharmaceuticals LP filed an answer and counterclaims on November 5, 2021, including claims challenging the asserted patents as not infringed and/or invalid, and accusing plaintiffs of patent misuse. The parties stipulated to dismiss AstraZeneca PLC as a defendant and Pfizer as a Counterclaim Defendant on December 10, 2021, which the Court so ordered on December 13, 2021. Puma filed its answer to AstraZeneca's counterclaims on December 17, 2021, denying those claims. The case was recently reassigned to visiting Judge Matthew Kennelly of the Northern District of Illinois. The parties filed a joint status report about the case and attended a teleconference with the Court on February 9, 2022. The parties submitted a joint discovery plan and proposed schedule for consideration by the Court on February 15, 2022. On February 17, 2022, Judge Kennelly entered a schedule for the case, including setting the matter for trial to begin May 13, 2024. The parties will now proceed to fact discovery.

*Sandoz Litigation*

On November 10, 2021, Puma filed suit against Sandoz, Inc. for infringement of U.S. Patent No. 7,399,865 B2 ("the '865 patent") (*Puma Biotechnology, Inc. et al. v. Sandoz Inc.*, 1:21CV19918 (D.N.J. Nov. 10, 2021**)** in the U.S. District Court for the District of New Jersey. The Complaint was filed within 45 days of Sandoz providing notice of its abbreviated new drug application ("ANDA") seeking approval to market a generic version of Puma's NERLYNX (neratinib) Tablets, 40 mg prior to the expiration of the '865 patent. Puma and Wyeth seek judgment that Sandoz's purported ANDA product would, if allowed on the market, infringe the '865 patent, and ask that the Court order that, pursuant to 35 U.S.C. 271(e)(4)(A), the FDA's approval of the Sandoz NDA can be no earlier than the date the '865 patent expires. Sandoz has stated that, due to Paragrah III certifications filed for other patents listed in the Orange Book in conjunction with NERLYNX. Sandoz cannot launch its ANDA product until November 30, 2030 at the earliest. Puma's complaint alleges

that Sandoz has infringed the '865 patent by seeking approval to commercially manufacture, use, offer for sale, sell, and/or import a generic version of NERLYNX in the United States prior to the expiration of the '865 patent. Puma is the exclusive licensee of the '865 patent under the Pfizer Agreement. Wyeth is a co-plaintiff. Sandoz submitted its answer to the complaint on January 14, 2022, and asserted counterclaims challenging the '865 patent as invalid. Puma and Wyeth filed an answer to those counterclaims on February 4, 2022. The parties appeared before the Magistrate Judge on February 15, 2022 for an initial hearing, and submitted a scheduling order on February 18, 2022. The filing of Puma's Complaint against Sandoz triggered a 30-month stay of marketing approval for Sandoz's ANDA.

*China Litigation*

On January 18, 2022, Shanghai Acebright Pharmaceuticals Group Co., Ltd. ("Acebright") filed an ANDA with the National Medical Products Administration in China ("NMPA") seeking approval to market a generic version of Puma's NERLYNX (neratinib) tablet, 40mg in China. Acebright seeks approval prior to the expiration of three patents listed on the China Patent Information Registration Platform for Marketed Drugs ("Chinese Orange Book"), namely, Chinese Patent Nos. ZL201410082103.7, ZL201080060546.6, and ZL200880118789.3 ("NERLYNX Patents"), alleging in a Type 4.2 patent declaration that its generic version of NERLYNX does not fall within the scope of the claims of NERLYNX Patents listed on the Chinese Orange Book. The patent declaration of Acebright were published on the Chinese Orange Book on January 19, 2022. Puma and/or its commercialization partner in China have 45 days from the publication of the patent declarations of Acebright to request administrative or judicial determination that Acebright's generic neratinib tablet falls within the scope of the claims of NERLYNX Patents listed on the Chinese Orange Book. Upon acceptance of the request for administrative or judicial determination, NMPA will institute a stay of Acebright's ANDA for nine months. If, during the nine-month stay period, an administrative or judicial determination is made that Acebright's generic neratinib tablet falls within the scope of the claims of the NERYLYNX Patents listed on the Chinese Orange Book, NMPA will be prohibited from approving Acebright's ANDA until the NERLYNX Patents expire.

**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, under the symbol "PBYI" since January 3, 2017. Prior to January 3, 2017, shares of our common stock had been listed on the New York Stock Exchange since October 19, 2012.

### Record Holders

On February 25, 2022, we had nine 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 11,000 additional owners held our common stock in "Street Name" as of February 25, 2022.

### 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 Note Purchase Agreement with Athyrium.

### 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 2021.

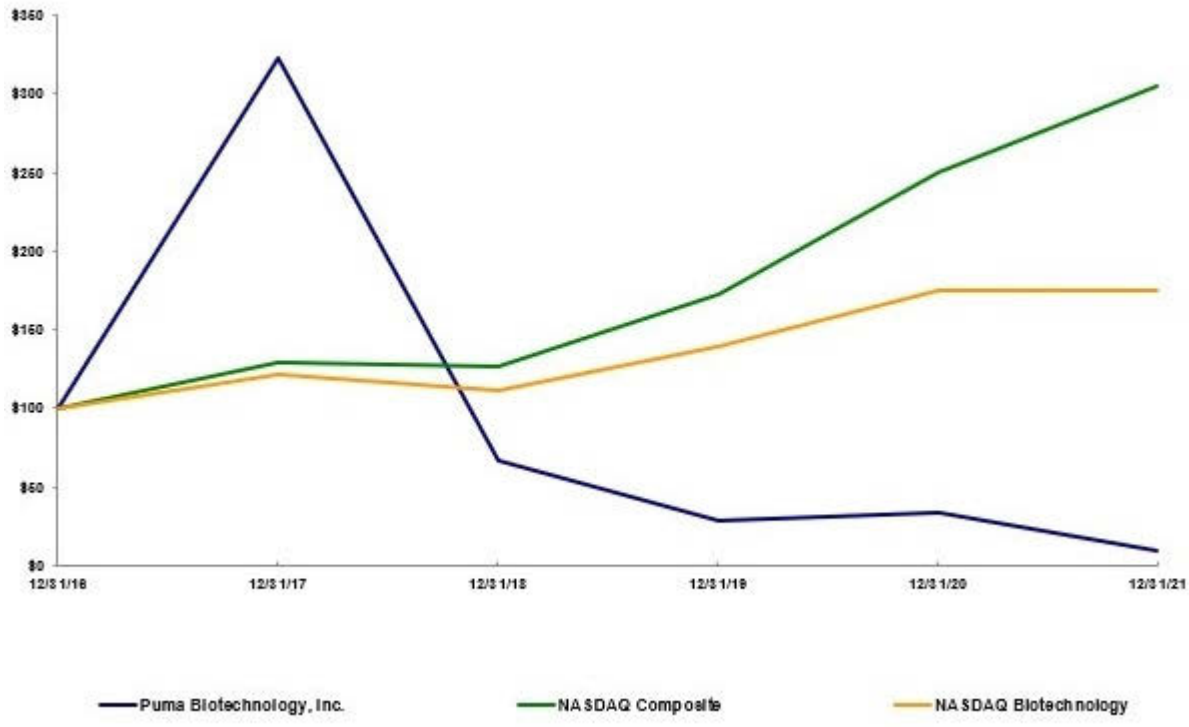
### Purchases of Equity Securities by the Issuer and Affiliated Purchasers

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 2021.

**Puma Biotechnology, Inc. (PBYI)***
**Stock Price Performance Graph**

The graph and table below compare the cumulative total return of our common stock from December 31, 2016, through December 31, 2021, with the cumulative total returns on (i) the Nasdaq Biotechnology Index and (ii) the Nasdaq Composite Index. The comparison assumes investment of $100 on December 31, 2016, 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.




| | 12/31/16 | 12/31/17 | 12/31/18 | 12/31/19 | 12/31/20 | 12/31/21 |
|---|---|---|---|---|---|---|
| **Puma Biotechnology, Inc.** | **100.00** | **321.99** | **66.29** | **28.50** | **33.42** | **9.90** |
| **NASDAQ Composite Index** | **100.00** | **129.64** | **125.96** | **172.17** | **249.51** | **304.85** |
| **NASDAQ Biotechnology Index** | **100.00** | **121.63** | **110.85** | **138.69** | **175.33** | **175.37** |

* On October 19, 2012, shares of Puma common stock were listed and began trading on the New York Stock Exchange. On January 3, 2017, the listing of shares of Puma common stock was moved to the Nasdaq Stock Market.

**ITEM 6. [RESERVED]**

## 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-licensed from Pfizer, Inc. ("Pfizer") the global development and commercialization rights to PB272 (neratinib, oral), PB272 (neratinib, intravenous) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor ("TKI") that blocks signal transduction through the human epidermal growth factor receptors, HER1, HER2 and HER4. Currently, we are primarily focused on the development and commercialization of the oral version of neratinib, our most advanced drug candidate is directed at the treatment of HER2-positive breast cancer and HER2 mutated cancers. We believe neratinib has clinical application in the treatment of several other cancers as well, including other tumor types that over-express or have a mutation in HER2 or EGFR, such as breast cancer, cervical cancer, lung cancer or other solid tumors.

Prior to 2017, our efforts and resources had been focused primarily on acquiring and developing our pharmaceutical technologies, raising capital and recruiting personnel. In 2017, the U.S. Food and Drug Administration ("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 adjuvant trastuzumab-based therapy. In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. In 2018, the European Commission ("EC"), granted marketing authorization for NERLYNX in the European Union for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy.

We have entered into exclusive sub-license agreements with various parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved, in numerous regions outside the United States, including Europe (excluding Russia and Ukraine), Australia, Canada, China, Southeast Asia, Israel, Mexico, South Korea, and various countries and territories in Central and South America. We plan to continue to pursue commercialization of NERLYNX in other countries outside the United States, if approved.

In July 2021, we announced that the U.S. Food and Drug Administration ("FDA") approved a labeling supplement to the U.S. Prescribing Information for NERLYNX that incorporates the use of NERLYNX dose escalation as evaluated in the Phase II CONTROL Trial. In July 2021, our Canadian partner, Knight Therapeutics, Inc., received Health Canada's approval of an alternate dosing regimen (two-week dose escalation) to be incorporated into the prescribing information.

On July 23, 2021, we entered into a note purchase agreement with Athyrium Opportunities IV Co-Invest 1 LP ("Athyrium") for an aggregate principal amount of $100.0 million. The borrowings under the Athyrium Note Purchase Agreement ("Athyrium Notes"), together with cash on hand, were used to repay the outstanding indebtedness, including the applicable exit and prepayment fees owed to lenders under our Oxford Credit facility. See Note 10-Debt, for further details regarding both the Athyrium Notes and Oxford Loan and Security Agreement.

In the fourth quarter of 2021, Puma received additional approvals for the use of NERLYNX in the extended adjuvant population. On November 11, 2021, Bixink's, Puma's partner in South Korea announced the approval of NERLYNX from the Korean Ministry of Food and Drug Safety and on December 13, 2021, Pint Pharma, Puma's partner in Latin America announced that the Brazilian Health Authority ("ANVISA") had approved NERLYNX in Brazil.

In December 2021, NERLYNX (neratinib) was included in the updated National Reimbursement Drug List ("NRDL") by the China National Healthcare Security Administration ("NHSA") for patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer after adjuvant trastuzumab based therapy. The addition of NERLYNX to the China NRDL now enables broad access to neratinib to more women throughout China.

Our expenses to date have been related to hiring staff, commencing company-sponsored clinical trials and the build out of our corporate infrastructure and, since 2017, the commercial launch of NERLYNX. Accordingly, our success depends not only on the safety and efficacy of our product candidates, but also on our ability to finance product development. To date, our major sources of working capital have been proceeds from product and license revenue, public offerings of our common stock, proceeds from various debt instruments and sales of our common stock in private placements.

**Impact of COVID-19**

Our priorities during the COVID-19 pandemic are protecting the health and safety of our employees while continuing our mission to develop and commercialize innovative products to enhance cancer care. Substantially all geographic regions in which our U.S. sales force operates have imposed, and those regions or other regions in which our sales force operates may in the future impose, “shelter-in-place” orders, quarantines or similar orders or restrictions to control the spread of COVID-19. These types of restrictions may deter or prevent cancer patients from traveling to see their doctors and result in a decline in revenue for NERLYNX, our only commercial product. Additionally, our commercial team and sales force have limited travel and personal interactions with physicians and customers, including visits to healthcare provider offices due to limitations that have been imposed at certain hospitals and medical facilities, and are currently conducting a large percentage of promotional activities virtually. These types of restrictions have adversely impacted our ability to engage with our customers and have adversely impacted sales of NERLYNX, our only commercial product, and they may continue to do so. The respective commercial teams of certain of the companies to which we sub-license the commercial rights to NERLYNX, and on which we rely for our international sales, have chosen or have been forced to take similar action, and other sub-licensees of NERLYNX may choose or be forced to take similar action. Furthermore, the COVID-19 pandemic has resulted in dramatic increases in unemployment rates, which may result in a substantial number of people becoming uninsured or underinsured. Any of these developments may have an adverse effect on our revenue. We have observed disruptions in patient enrollments in the United States and in our SUMMIT basket trial. If the COVID-19 pandemic continues to spread in the geographies in which we are conducting clinical trials, we may experience additional disruptions in those clinical trials, which could have a material adverse impact on our clinical trial plans and timelines.

Our ability to continue to operate without any significant negative impacts will in part depend on the length and severity of the COVID-19 pandemic and our ability to protect our employees and our supply chain. We continue to follow and monitor recommended actions of government and health authorities to protect our employees worldwide. For the year ended December 31, 2021, we and our key third-party suppliers and manufacturers were able to broadly maintain operations. We rely exclusively on third-party manufacturers to manufacture NERLYNX.

We intend to satisfy our near-term liquidity requirements through a combination of our existing cash and cash equivalents and marketable securities as of December 31, 2021 and proceeds that will become available to us through product sales, royalties and sub-license milestone payments. However, this intention is based on assumptions that may prove to be wrong. Changes may occur that would consume our available capital faster than anticipated, including the length and severity of the COVID-19 pandemic and measures taken to control the spread of COVID-19, as well as changes in and progress of our development activities, the impact of commercialization efforts, acquisitions of additional drug candidates and changes in regulation. Some of these developments have had and may continue to have an adverse effect on our revenue and thus could have an adverse effect on our ability to satisfy the minimum revenue and cash balance covenants in our loan and security agreement.

**Key Litigation Developments**

On October 29, 2021, the parties to the class action lawsuit against us and certain of our executive officers, *Hsu v. Puma Biotechnology, Inc., et. al.,* informed the court that a settlement was reached in principle. The court entered judgment in an amount representing the claimed damages and prejudgment interest totaling approximately $54.2 million. On November 2, 2021, the court dismissed the case in light of the parties' settlement and retained jurisdiction solely for the purpose of settlement approval. The parties' settlement in principle provides that there will be no judgment for liability entered against us or Mr. Auerbach, and additionally provides for payment by us of approximately $54.2 million in two (2) installments payable in January 2022 and June 2022. The settlement in principle is subject to execution of a formal settlement agreement to be negotiated among the parties, which will be submitted to the court for approval. For additional detail regarding the class action lawsuit, see Part I. Item 3. Legal Proceedings in this Annual Report on Form 10-K.

In February 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 alleged that we and Mr. Auerbach made defamatory statements regarding Dr. Eshelman in connection with a proxy contest. In May 2016, Dr. Eshelman filed a notice of voluntary dismissal of the claims against Mr. Auerbach. A trial on the remaining defamation claims against us took place from March 11 to March 15, 2019. At trial, the jury found us liable and awarded Dr. Eshelman $15.9 million in compensatory damages and $6.5 million in punitive damages. We strongly disagreed with the verdict and, on April 22, 2019, filed a motion for a new trial or, in the alternative, a reduced damages award. The Court denied that motion on March 2, 2020. We appealed that ruling, and the verdict. Additionally, after trial, the plaintiff filed a motion seeking approximately $3.0 million in attorneys' fees, as well as prejudgment interest. In the Court's March 2, 2021 ruling, it denied the motion for attorneys' fees but granted the request for prejudgment interest, bringing the total judgment to $26.3 million. On March 30, 2020, the plaintiff filed a notice of cross-appeal and conditional cross-appeal, appealing the Court's order denying the plaintiff's request for attorneys' fees and conditionally cross-appealing a Court ruling that certain communications between Mr. Auerbach and his attorneys were protected by attorney-client privilege and a related evidentiary ruling. On June 23, 2021, the United States Court of Appeals for the Fourth Circuit affirmed the liability verdict in the Eshelman v. Puma Biotechnology, et. al matter but found the $22.4 million damages award, payable by us, to be excessive in light of the evidence at trial. The court vacated this award and remanded for a new trial on damages. The Court's judgment will eliminate the damages award, including interest on the judgment, pending further proceedings on remand. On July 7, 2021, the plaintiff filed a petition for panel or en banc rehearing, which was denied on July 20, 2021. On July 26, 2021, the plaintiff filed a motion to stay issuance of the Fourth Circuit's mandate pending the filing and resolution of a petition for certiorari in the Supreme Court. The Fourth Circuit denied that motion on July 29, 2021. On October 18, 2021, the plaintiff filed a petition of certiorari with the Supreme Court seeking review of the Fourth Circuit's ruling. On December 13, 2021, the Supreme Court denied plaintiff's petition for certiorari. The case remains pending in the district court, which has not yet scheduled the new trial on damages.

**Summary of Income and Expenses**

*Product revenue, net*

Product revenue, net consists of revenue from sales of NERLYNX. We sell NERLYNX to a limited number of specialty pharmacies and specialty distributors in the United States. 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 earned for performance obligations satisfied pursuant to our sub-license agreements.

*Royalty revenue*

Royalty revenue consists of consideration earned related to product sales made by our sub-licensees in their respective territories 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 also includes period costs related to royalty charges payable to Pfizer, the amortization of milestone payments under our license agreement with Pfizer, certain inventory manufacturing services, inventory adjustment charges, unabsorbed manufacturing and overhead costs, and manufacturing variances. Cost of license revenue includes applicable license termination fees.

*Selling, general and administrative expenses*

Selling, general and administrative ("SG&A") expenses, consist primarily of salaries and payroll-related costs, stock-based compensation expense, professional fees, business insurance, rent, general legal activities, credit loss expense and other corporate expenses. We expense SG&A expenses as they are incurred.

*Research and development expenses*

Research and development ("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, 2021, 2020 and 2019, our R&D expenses consisted primarily of CRO fees; fees paid to consultants; salaries and related personnel costs; and stock-based compensation. We expense our R&D expenses as they are incurred. Internal R&D expenses primarily consist of payroll-related costs and also include equipment costs, travel expenses and supplies.

**Results of Operations**

The following summarizes our results of operations for the years ended December 31, 2021 and 2020. For discussion related to the results of operations and changes in financial condition for the year ended December 31, 2020 compared to the year ended December 31, 2019, please refer to Item 7 of Part II, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report for the Year Ended December 31, 2020, which was filed with the United States Securities and Exchange Commission on March 1, 2021.

*Total revenue*

Total revenue was approximately $253.2 million for the year ended December 31, 2021, compared to $225.1 million for the year ended December 31, 2020.

*Product revenue, net*

Product revenue, net was approximately $189.1 million for the year ended December 31, 2021, compared to $196.7 million for the year ended December 31, 2020. The decrease in product revenue, net was attributable to a volume decrease of approximately 13% in bottles of NERLYNX sold, and an increase in reserves for variable consideration from approximately 16% of product revenue for the year ended December 31, 2020 to approximately 19% of product revenue for the year ended December 31, 2021. The increase in reserves for variable consideration is primarily due to an increase in Medicaid claims and government chargebacks as a percentage of gross revenue. The decrease in product revenue, net was partially offset by increases in gross selling price that occurred in the first and third quarters of 2021.

*License revenue*

License revenue was approximately $51.8 million for the year ended December 31, 2021, compared to $22.7 million for the year ended December 31, 2020. The increase in license revenue was primarily due to a large upfront payment resulting from an amendment to a sub-licensing agreement during the year ended December 31, 2021.

*Royalty revenue*

Royalty revenue was approximately $12.3 million for the year ended December 31, 2021, compared to $5.7 million for the year-ended December 31, 2020. The increase was due to increased product sales by our sub-licensees as they increased commercialization of NERLYNX in additional territories.

*Cost of sales*

Cost of sales was approximately $63.7 million for the year ended December 31, 2021, compared to $39.4 million for the year ended December 31, 2020. The increase in cost of sales was primarily attributable to a one-time license termination fee of $20.0 million in February 2021 and increased royalty and license fee expenses of $3.5 million.

*Selling, general and administrative expenses:*

| **Selling, general, and administrative expenses (in thousands)** | **For the Year Ended December 31,** | | **Change** | |
|---|---|---|---|---|
| | | | **$** | **%** |
| | **2021** | **2020** | **2021/2020** | **2021/2020** |
| Payroll and related costs | $ 38,118 | $ 41,313 | $ (3,195) | -7.7% |
| Professional fees and expenses | 38,356 | 42,935 | (4,579) | -10.7% |
| Travel and meetings | 4,521 | 4,726 | (205) | -4.3% |
| Facilities and equipment costs | 5,546 | 5,673 | (127) | -2.2% |
| Stock-based compensation | 25,699 | 17,778 | 7,921 | 44.6% |
| Credit loss expense (recovery) | (1,000) | 1,000 | (2,000) | -200.0% |
| Other | 5,054 | 5,063 | (9) | -0.2% |
| | $ 116,294 | $ 118,488 | $ (2,194) | -1.9% |

Total SG&A expenses decreased approximately 1.9% to $116.3 million for the year ended December 31, 2021 from $118.5 million for the year ended December 31, 2020. The decrease is primarily attributable to the following:

- a decrease in payroll and related costs of approximately $3.2 million due to a reduction in headcount;
- a decrease in professional fees and expenses of approximately $4.6 million, consisting of a $5.7 million decrease in consulting fees related to marketing and commercialization efforts, partially offset by an increase of $1.1 million in legal fees;
- a recovery of credit loss expense of $1.0 million for the year ended December 31, 2021, compared to a credit loss expense of $1.0 million for the year ended December 31, 2020;

which were partially offset by:

- an increase in stock-based compensation expense of approximately $7.9 million primarily due to the $13.6 million incremental expense resulting from the modification of the term of Mr. Auerbach's warrant, and an increase of approximately $4.0 million from new grants, partially offset by a decrease of approximately $7.9 million for fully vested grants and a decrease of approximately $1.8 million for awards forfeited.

*Research and development expenses:*

| **Research and development expenses (in thousands)** | **For the Year Ended December 31,** | | **Change** | |
|---|---|---|---|---|
| | | | **$** | **%** |
| | **2021** | **2020** | **2021/2020** | **2021/2020** |
| Clinical trial expense | $ 26,033 | $ 31,428 | $ (5,395) | -17.2% |
| Internal R&D | 33,068 | 38,736 | (5,668) | -14.6% |
| Consultant and contractors | 5,835 | 8,689 | (2,854) | -32.8% |
| Stock-based compensation | 6,934 | 18,797 | (11,863) | -63.1% |
| | $ 71,870 | $ 97,650 | $ (25,780) | -26.4% |

Total R&D expenses decreased approximately 26.4% to $71.9 million for the year ended December 31, 2021 from approximately $97.7 million for the year ended December 31, 2020. The decrease is primarily attributable to the following:

- a decrease in stock-based compensation expense of approximately $11.9 million related to the full vesting of previous grants;
- a decrease in internal R&D expense of approximately $5.7 million as a result of lower headcount and related compensation expense;
- a decrease in clinical trial expenses of approximately $5.4 million due to the close out of certain clinical trials and a reduction in patient enrollments and monitoring costs; and
- a decrease in consultant and contractor expenses of approximately $2.9 million due to the close out of certain clinical trials.

*Other income and expenses:*

| **Other income (expenses) (in thousands)** | **For the Year Ended December 31,** | | **Change** | |
|---|---|---|---|---|
| | | | **$** | **%** |
| | **2021** | **2020** | **2021/2020** | **2021/2020** |
| Interest income | $ 160 | $ 489 | $ (329) | -67.3% |
| Interest expense | (12,807) | (14,046) | 1,239 | -8.8% |
| Legal verdict expense | (9,591) | (16,196) | 6,605 | -40.8% |
| Loss on debt extinguishment | (8,146) | — | (8,146) | 100.0% |
| Other income | 292 | 367 | (75) | -20.4% |
| | $ (30,092) | $ (29,386) | $ (706) | 2.4% |

*Interest expense*

For the year ended December 31, 2021, we recognized approximately $12.8 million in interest expense compared to approximately $14.0 million of interest expense for the year ended December 31, 2020. The approximately $1.2 million decrease in interest expense is primarily due to less interest expense related to Pfizer in 2021.

*Legal verdict expense*

For the year ended December 31, 2021, we reduced our legal verdict expense accrual by approximately $19.8 million with respect to the Eshelman v. Puma Biotechnology, Inc., et.al judgment, and we increased our legal verdict expense accrual by approximately $29.4 million with respect to the *Hsu v. Puma Biotechnology, Inc., et. al* judgement, which resulted in a net legal verdict expense of approximately $9.6 million for the period.

*Loss on debt extinguishment*

For the year ended December 31, 2021 we recognized approximately $8.1 million in loss on debt extinguishment in connection with our debt refinancing during the third quarter of 2021. See Note 10-Debt.

**Non-GAAP Financial Measures:**

In addition to our operating results, as calculated in accordance with U.S. 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 income (loss) and net income (loss) per share, as calculated in accordance with GAAP, as adjusted to remove the impact of stock-based compensation. For the years ended December 31, 2021 and 2020, stock-based compensation represented approximately 112.0% and 61.0% of our net loss, respectively. Our management believes that these non-GAAP financial measures are useful to 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 Income (Loss) and GAAP Net Loss Per Share to Non-GAAP Adjusted Net Income (Loss) Per Share**
**(in thousands except share and per share data)**

| | For the Year Ended December 31, | |
|---|---|---|
| | 2021 | 2020 |
| GAAP net loss | $ (29,126) | $ (59,995) |
| Adjustments: | | |
| Stock-based compensation - | | |
| Selling, general and administrative | 25,699 | 17,778(1) |
| Research and development | 6,934 | 18,797(2) |
| Non-GAAP adjusted net income (loss) | $ 3,507 | $ (23,420) |
| | | |
| GAAP net loss per share—basic | $ (0.72) | $ (1.52) |
| Adjustment to net loss (as detailed above) | 0.81 | 0.93 |
| Non-GAAP adjusted basic net income (loss) per share | $ 0.09 | $ (0.59)(3) |
| | | |
| GAAP net income (loss) per share—diluted | $ (0.70) | $ (1.52) |
| Adjustment to net income (loss) (as detailed above) | 0.78 | 0.93 |
| Non-GAAP adjusted diluted net income (loss) per share | $ 0.08(4) | $ (0.59)(5) |

(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 basic net loss per share was calculated based on 40,638,852 and 39,576,107 weighted-average shares of common stock outstanding for the years ended December 31, 2021 and 2020, respectively.
(4) Non-GAAP adjusted diluted net income per share was calculated based on 41,558,838 weighted average common shares outstanding and potentially dilutive common stock equivalents (stock options, restricted stock units and warrants) for the twelve months ended December 31, 2021.
(5) Potentially dilutive common stock equivalents (stock options, restricted stock units and warrants) were not included in the non-GAAP adjusted diluted net loss per share for the twelve months ended December 31, 2020 as these shares would be considered anti-dilutive.

**Liquidity and Capital Resources**

The following table summarizes our liquidity and capital resources as of and for the years ended December 31, 2021 and December 31, 2020 and is intended to supplement the more detailed discussion that follows:

| Liquidity and capital resources (in thousands) | As of December 31, 2021 | As of December 31, 2020 |
|---|---|---|
| Cash and cash equivalents | $ 63,131 | $ 85,293 |
| Marketable securities | 18,975 | 8,096 |
| Working capital | 30,436 | 31,884 |
| Stockholders' deficit | (2,446) | (5,951) |

| | Year Ended December 31, 2021 | Year Ended December 31, 2020 |
|---|---|---|
| Cash provided by (used in): | | |
| Operating activities | $ 20,650 | $ 773 |
| Investing activities | (10,881) | 33,403 |
| Financing activities | (31,931) | (9,932) |
| Net increase (decrease) in cash, cash equivalents and restricted cash | $ (22,162) | $ 24,244 |

*Operating Activities*

We recorded net losses of approximately $29.1 million and approximately $60.0 million for the years ended December 31, 2021 and 2020, respectively. We recorded positive cash flows from operating activities of approximately $20.7 million for the year ended December 31, 2021 and recorded positive cash flows from operating activities of approximately $0.8 million for the year ended December 31, 2020.

Net cash provided by operating activities for the year ended December 31, 2021 consisted of a net loss of a $29.1 million, offset by a decrease of non-cash items of approximately $46.6 million, including stock-based compensation, depreciation and amortization, credit loss recovery and loss on extinguishment of debt of approximately $3.8 million related to the write off of debt issuance costs. Further changes in cash flows from operations included an increase in accrued expenses other of approximately $5.2 million, a decrease in other current assets of approximately $3.2 million, and a decrease in prepaid expenses and other of approximately $2.7 million. These changes were offset by an increase in accounts receivable, net of approximately $6.0 million, a increase in inventory of approximately $3.7 million, a decrease in post-marketing commitment liability of approximately $1.1 million, and a decrease in accounts payable of approximately $0.9 million.

Net cash used in operating activities for the year ended December 31, 2020, included a net loss of approximately $60.0 million, adjusted for non-cash items of approximately $36.6 million for stock-based compensation expense, approximately $10.0 million for depreciation and amortization, and $1.0 million for a provision for credit loss expense. Further changes in cash flows from operations included an increase in accrued expenses of approximately $19.3 million, a decrease in accounts receivable, net of approximately $2.4 million, and a decrease in prepaid expenses and other of approximately $2.3 million. These changes were offset by a decrease in accounts payable of approximately $7.1 million, an increase in other current assets of approximately $3.1 million, and an increase in inventory, net of approximately $0.3 million, and other immaterial fluctuations.

*Investing Activities*

During the year ended December 31, 2021, cash provided by investing activities was approximately $10.9 million. This included the maturity of available-for-sale securities of approximately $27.2 million, partially offset by the purchase of available-for-sale securities of approximately $38.1 million.

During the year ended December 31, 2020, cash provided by investing activities was approximately $33.4 million. This included the maturity of available-for-sale securities of approximately $73.2 million, partially offset by the purchase of available-for-sale securities of approximately $29.8 million and an increase in intangible assets relating to the milestone achieved under our license agreement with Pfizer of $10.0 million.

*Financing Activities*

During the year ended December 31, 2021, cash provided by financing activities was approximately $31.9 million. During July 2021, we used approximately $8.5 million for the payment of prepayment costs, end of loan payment costs and other extinguishment costs related to our credit facility with Oxford, and approximately $1.9 million in payment of debt issuance costs related to the Athyrium Notes, and $20.0 million was used for installment payments relating to the milestone achieved under our license agreement with Pfizer of $20.0 million.

During the year ended December 31, 2020, cash used in financing activities was approximately $9.9 million related to the installment payment associated with a milestone achieved under our license agreement with Pfizer of $10.0 million. Additionally, during April 2020, approximately $8.4 million was borrowed and fully repaid with no penalty or interest from Silicon Valley Bank, ("SVB") under the Paycheck Protection Program ("PPP"), of the Coronavirus Aid, Relief, and Economic Security Act.

*Oxford Loan and Security Agreement*

In October 2017, we initially entered into a loan and security agreement with SVB, as administrative agent, and the lenders party thereto from time to time, or the Original Lenders, including Oxford and SVB (as amended and restated from time to time, the "Oxford Credit Facility"). On February 3, 2021, we amended the Oxford Credit Facility to establish revised minimum revenue thresholds for the trailing year to date periods ending March 31, June 30, September 30, and December 31, 2021. Pursuant to the terms of the Oxford Credit Facility, at our option, we could prepay the outstanding principal balance of any term loan in whole, but not in part, subject to a prepayment fee of either (a) three percent (3.0%) of the amount prepaid if the prepayment occurred through and including the first anniversary of the funding date of such term loan, (b) two percent (2.0%) of the amount prepaid if the prepayment occurred 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, or (c) one percent (1.0%) of the amount prepaid if the prepayment occurred after the second anniversary of the funding date of such term loan and prior to the Maturity Date. On July 23, 2021, we used proceeds from the Athyrium Note Purchase Agreement to repay the amounts outstanding under the Oxford Credit Facility, together with applicable exit and prepayment fees, and terminated the Oxford Credit Facility.

*Athyrium Note Purchase Agreement*

We issued senior notes for an aggregate principal amount of $100.0 million pursuant to the note purchase agreement dated July 23, 2021, by us, and our subsidiaries, and Athyrium, as Administrative Agent, and certain other investor parties (the "Note Purchase Agreement"), with an initial maturity date of July 23, 2026 (the "Athyrium Notes"). The Athyrium Notes were issued for face amount of $100.0 million net of an original issue discount of $1.5 million. The Athyrium Notes also require a 2.0% exit payment to be made on each payment of principal. The borrowings under the Athyrium Notes, together with cash on hand, were used to repay our outstanding indebtedness, including the applicable exit and prepayment fees owed to lenders under its Oxford Credit Facility. We can borrow up to an additional $25.0 million under the Note Purchase Agreement for general corporate purposes and to further support commercial initiatives. The Athyrium Notes are secured by substantially all of our assets. We incurred $1.9 million of deferred financing costs with the borrowing.

The Athyrium Notes bear interest at an annual rate equal to the sum of (i) 8.0% and (ii) three-month London Interbank Offering Rate ("LIBOR") rate where the three-month LIBOR rate cannot be less than 1.5% or greater than 3.5%. (or a comparable or successor rate that gives due consideration to the then prevailing rate used by commercial banks in the United States which rate is reasonably determined by Athyrium). Interest is payable quarterly on the last business day of March, June, September and December each year. Beginning June 30, 2024, principal payments are required to be made quarterly at 11.11% of the original face amount with the remaining balance paid at maturity. Each principal payment will also include a 2.0% exit payment. As of December 31, 2021, the effective interest rate for the loan was 10.98%.

At the Company's option, the Company may prepay the outstanding principal balance of the notes in whole or in part, subject to a prepayment fee of 2.0% of the amount prepaid if the prepayment occurs on or prior to the second anniversary of the issuance date of such notes, plus the present value of remaining interest that would have accrued through and including the second anniversary date, and 2.0% of the amount prepaid if the prepayment occurs after the second anniversary but on or prior to the third anniversary of the issuance date of such notes.

The Athyrium Notes include affirmative and negative covenants applicable to the Company. The affirmative covenants include, among others, covenants requiring the Company to maintain its legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, and satisfy certain requirements regarding deposit accounts. The negative covenants include, among others, restrictions on the Company's 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 Company is also required to achieve certain minimum product revenue targets, measured as of the last day of each fiscal quarter on a trailing year-to-date basis.

As of December 31, 2021, the principal balance outstanding under the Athyrium Notes was $100.0 million, representing all of the Company's long-term debt. The Company was in compliance with all applicable covenants under the Athyrium Notes.

*Current and Future Financing Needs*

We did not receive or record 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 our commercialization efforts.

We may choose to begin new R&D efforts or we may choose to launch additional marketing efforts. These efforts may require funding in addition to the cash and cash equivalents totaling approximately $63.1 million and approximately $19.0 million in marketable securities available at December 31, 2021. 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 need to generate significant revenue to sustain operations and successfully commercialize 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, including the global COVID-19 pandemic, our success in commercializing neratinib, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time. We believe that our existing cash and cash equivalents and marketable securities as of December 31, 2021 and proceeds that will become available to us through product sales and sub-license payments are sufficient to satisfy our operating cash and capital needs for at least one year after the filing of this Annual Report.

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. 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.

**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 leases for office space and office equipment and the principal and interest owed under our Note Purchase Agreement. We also have unrecognized tax benefits that, if recognized, would affect the effective tax rate at December 31, 2021. 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, 2021, aggregated by type (in thousands):

| Contractual Obligations | Total | Less than 1 year | 1 - 3 years | 3 - 5 years | More than 5 years |
|---|---|---|---|---|---|
| Operating lease obligations | $ 24,410 | $ 5,483 | $ 11,436 | $ 7,491 | — |
| Debt obligations (principal and interest) | 135,782 | 9,632 | 52,478 | 73,672 | — |
| Total | **$ 160,192** | **$ 15,115** | **$ 63,914** | **$ 81,163** | — |

We also engage with CROs and contract manufacturing organizations ("CMOs") in addition to engaging in contracts for the management of its ongoing clinical trials and pre-commercialization efforts. The Company may cancel these agreements with a 30 to 45 day written notice to the outside vendor. We would be obligated to pay for services rendered up to that point, which amounts to total contractual obligations of $54.8 million within the next twelve months. The contracts also contain variable costs that are hard to predict as they are based on such things as patients enrolled and clinical trial sites, which can vary, and therefore, are not included in the total obligations amount.. Included in the total contractual obligations above are payments to be made when milestones are reached. As of December 31, 2021, our obligations for potential milestone payments totaled approximately $17.3 million. This amount will be paid by the Company if all milestones are reached and would reduce the overall contractual obligation if one or more milestone is never reached.

In regard to our contractual obligations in relation to the Pfizer in-license agreement, as consideration for the license, we are required to make substantial payments upon the achievement of certain milestones totaling approximately $187.5 million if all such milestones are achieved. The remaining milestone amounts were not included in the table above as the timing of when or if these payments will be made is uncertain. In connection with the FDA approval of NERLYNX in July of 2017, we triggered a one-time milestone payment pursuant to the agreement. In June 2020, we entered into a letter agreement with Pfizer relating to the method of payment associated with a milestone payment under our license agreement with Pfizer (see Note 14-Commitments and Contingencies in the accompanying notes to the financial statements). Should we commercialize any more of the compounds licensed from Pfizer or any products containing any of these compounds, we will be obligated to pay to Pfizer annual royalties at a fixed rate in the low to mid-teens of net sales of all such products, subject to certain reductions and offsets in some circumstances. Our royalty obligation continues, on a product-by-product and country-by-country basis, until the later of (i) the last to expire 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 in such country or expiration of a certain time period after first commercial sale of such licensed product in such country. In the event that we sublicense the rights granted to us under the license agreement with Pfizer to a third party, the same milestone and royalty payments are required. We can terminate the license agreement at will, or for safety concerns, in each case upon specified advance notice.

See Note 13-Income Taxes and Note 14-Commitments and Contingencies in the accompanying notes to the financial statements for a summary of our uncertain tax positions and contracts held by us as of December 31, 2021. As of December 31, 2021, the amount of unrecognized tax benefit was $4.3 million, and is also not included in the table above as the timing of when or if these payments will be made is uncertain.

**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***

Under Accounting Standards Codification ("ASC") Topic 606 - *Revenue from Contracts with Customers ("*ASC 606") we recognize revenue when a customer obtains control of the promised goods or services, in an amount that reflects the consideration which we expect 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 and specialty distributors in the United States to distribute NERLYNX. These arrangements are our initial contracts with customers. We have determined that these sales channels with customers are similar.

***Product Revenue, Net:***

We sell NERLYNX to a limited number of specialty pharmacies and specialty distributors in the United States. These customers subsequently resell our products to patients and certain medical centers or hospitals. In addition to distribution agreements with these customers, we enter into arrangements with health care providers and payors that provide for government mandated and/or privately negotiated rebates, chargebacks and discounts with respect to the purchase of our products.

We recognize revenue on product sales when the specialty pharmacy or specialty distributor, as applicable, obtains control of our product, which occurs at a point in time (upon delivery). Product revenue is recorded net of applicable reserves for variable consideration.

Shipping and handling costs for product shipments occur prior to the customer obtaining control of the goods and are recorded in cost of sales.

***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 ASC 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 significant reversal of revenue would not occur in a future period for the estimates detailed below as of December 31, 2021 and, therefore, the transaction price was not reduced further during the year ended December 31, 2021. 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.

***Product Returns:***

Consistent with industry practice, we offer the specialty pharmacies and specialty distributors 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 as a reduction to accounts receivables, net on the consolidated balance sheets. We currently estimate product returns using 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 a reduction to accounts receivable, net on the consolidated balance sheets. Chargeback amounts are generally determined at the time of resale to the qualified healthcare provider by customers, and we generally issue credits for such amounts within a few weeks of the customer's notification to us of the resale. Chargebacks consist of credits 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 on the consolidated balance sheets. 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 record 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 on the consolidated balance sheets.

***License Revenue:***

We recognize license revenue under certain of our sub-license agreements that are within the scope of ASC 606. The terms of these agreements may contain multiple performance obligations, which may include licenses and research and development activities. We evaluate these agreements under ASC 606 to determine the distinct performance obligations. Non-refundable, up-front fees that are not contingent on any future performance and require no consequential continuing involvement by us, are recognized as revenue when the license term commences and the licensed data, technology or product is delivered. We defer recognition of non-refundable upfront license fees if the performance obligations are not satisfied.

Prior to recognizing revenue, we make estimates of the transaction price, including variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Variable consideration may include nonrefundable upfront license fees, payments for research and development activities, reimbursement of certain third-party costs, payments based upon the achievement of specified milestones, and royalty payments based on product sales derived from the collaboration.

If there are multiple distinct performance obligations, we allocate the transaction price to each distinct performance obligation based on its relative standalone selling price. The standalone selling price is generally determined based on the prices charged to customers or using expected cost-plus margin. Revenue is recognized by measuring the progress toward complete satisfaction of the performance obligations using an input measure.

***Royalty Revenue:***

For sub-license agreements that are within the scope of ASC 606, we recognize revenue when the related sales occur in accordance with the sales-based royalty exception under ASC 606-10-55-65. Royalty revenue consists of consideration earned related to international sales of NERLYNX made by our sub-licensees in their respective territories. We recognize royalty revenue when the performance obligations have been satisfied.

***Legal Contingencies and Expense***

For legal contingencies, we accrue a liability for an estimated loss if the potential loss from any claim or legal proceeding is considered probable and the amount can be reasonably estimated. Legal fees and expenses are expensed as incurred based on invoices or estimates provided by legal counsel. We periodically evaluate available information, both internal and external, relative to such contingencies and adjust the accrual as necessary. We determine whether a contingency should be disclosed by assessing whether a material loss is deemed reasonably possible. In determining whether a loss should be accrued, we evaluate, among other factors, the degree of probability of an unfavorable outcome and the ability to make a reasonable estimate of the amount of the loss (see Note 14-Commitments and Contingencies in the accompanying notes to the financial statements).

**Recently Issued Accounting Standards**

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments.* ASU 2016-13 requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For trade accounts receivable, we recognize credit losses based on lifetime expected losses using the probability of default method. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. These amendments under ASU 2016-13 are effective for interim and annual fiscal periods beginning after December 15, 2019. We adopted ASU 2016-13, and the adoption did not have a material effect on our current financial position, results of operations or financial statement disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement*. As of January 1, 2020, we adopted the amendments in ASU 2018-13, which modifies the disclosure requirements on fair value measurements. The removed and modified disclosures were adopted on a retrospective basis and the new disclosures were adopted on a prospective basis. The adoption of ASU 2018-13 did not have a material effect on our current financial position, results of operations or financial statement disclosures.

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*, as part of its Simplification Initiative to reduce the cost and complexity in accounting for income taxes. The amendments in ASU 2019-12 remove certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also amends other aspects of the guidance to help simplify and promote consistent application of GAAP. The guidance is effective for interim and annual periods beginning after December 15, 2020, with early adoption permitted. We do not expect ASU 2019-12 to have a material effect on our current financial position, results of operations or financial statement disclosures.

## ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Some of the securities in which we invest 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, 2021. 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 notes sold pursuant to the Note Purchase Agreement (the "Notes"). As of December 31, 2021, the aggregate outstanding principal amounts of the Notes was $100.0 million. The Notes bear interest at a rate per annum equal to the sum of (a) 8.00% plus (b) the lesser of (x) three-month London Interbank Offered Rate ("LIBOR") and (y) 3.5% (or a comparable or successor rate that gives due consideration to the then prevailing rate used by commercial banks in the United States which rate is reasonably determined by Athyrium). If overall interest rates had increased by 100 basis points during the year ended December 31, 2021, our interest expense would have increased by $1.0 million.

## 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 Chief Financial Officer, 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 Chief Financial Officer, we have evaluated the effectiveness of our disclosure controls and procedures (as defined under Exchange Act Rule 13a-15(e)), as of December 31, 2021. Based on that evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that these disclosure controls and procedures were effective as of December 31, 2021.

### Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting that occurred during the year ended December 31, 2021, that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

**Management's Report on Internal Control over Financial Reporting**

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

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

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2021. 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, 2021, our internal control over financial reporting was effective.

Our internal control over financial reporting as of December 31, 2021 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, 2021.

## ITEM 9B. OTHER INFORMATION

None.

## ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

**Part III**

## ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item will be included in our 2022 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 2022 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 2022 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 2022 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 2022 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 Number | Description |
|---|---|
| 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 (filed as Exhibit 2.1 to the Company's Current Report on Form 8-K filed with the SEC on October 4, 2011 and incorporated herein by reference) |
| 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 (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K filed with the SEC on October 11, 2011 and incorporated herein by reference) |
| 3.2 | Certificate of Ownership and Merger relating to the merger of Puma Biotechnology, Inc. with and into Innovative Acquisitions Corp., filed with the Secretary of State of the State of Delaware on October 4, 2011 (filed as Exhibit 3.2 to the Company's Current Report on Form 8-K filed with the SEC on October 11, 2011 and incorporated herein by reference) |
| 3.3 | Second Amended and Restated Certificate of Incorporation of the Company, as filed with the Secretary of State of the State of Delaware on June 14, 2016 (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K filed with the SEC on June 15, 2016 and incorporated herein by reference) |
| 3.4 | Third Amended and Restated Bylaws of the Company (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K filed with the SEC on May 28, 2019 and incorporated herein by reference) |
| 4.1 | Form of Common Stock Certificate (filed as Exhibit 4.1 to the Company's Registration Statement on Form S-1/A filed with the SEC on February 1, 2012 and incorporated herein by reference) |
| 4.2# | Warrant to Purchase Shares of Common Stock of Puma Biotechnology, Inc., dated October 4, 2011, issued to Alan H. Auerbach (filed as Exhibit 4.2 to the Company's Current Report on Form 8-K filed with the SEC on October 11, 2011 and incorporated herein by reference) |
| 4.2(a)# | Amendment to Warrant to Purchase Shares of Common Stock of Puma Biotechnology, Inc., dated April 1, 2021, by and between the Company and Alan H. Auerbach (filed as Exhibit 4.1 to the Company's Current Report on Form 8-K filed with the SEC on June 17, 2021 and incorporated herein by reference) |
| 4.3 | Description of the Company's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934 (filed as Exhibit 4.3 to the Company's Annual Report on Form 10-K filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.1(a)* | License Agreement, dated August 18, 2011, by and between the Company, as successor to Puma Biotechnology, Inc., and Pfizer Inc. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K/A filed with the SEC on December 16, 2011 and incorporated herein by reference) |
| 10.1(b)* | Amendment No. 1 to License Agreement dated July 18, 2014, between the Company and Pfizer Inc. (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed with the SEC on November 10, 2014 and incorporated herein by reference) |
| 10.1(c)** | Pfizer Letter Agreement dated June 8, 2020, by and between the Company and Pfizer Inc. (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed with the SEC on August 6, 2020 and incorporated herein by reference) |
| 10.1(d)** | Amendment No. 2 to License Agreement dated October 29, 2020, between the Company and Pfizer Inc. (filed as Exhibit 10.1(d) to the Company's Annual Report on Form 10-K filed with the SEC on March 1, 2021 and incorporated by reference) |

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| 10.2(a)# | Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Exhibit 10.4 to the Company's Current Report on Form 8-K filed with the SEC on October 11, 2011 and incorporated herein by reference) |
| 10.2(b)# | First Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Appendix A to the Company's Proxy Statement on Form DEFR14A filed with the SEC on June 4, 2014 and incorporated herein by reference) |
| 10.2(c)# | Second Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed with the SEC on August 10, 2015 and incorporated herein by reference) |
| 10.2(d)# | Third Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on June 14, 2017 and incorporated herein by reference) |
| 10.2(e)# | Fourth Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K filed with the SEC on June 14, 2017 and incorporated herein by reference) |
| 10.2(f)# | Fifth Amendment to Puma Biotechnology, Inc. 2011 Incentive Award Plan (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on June 17, 2021 and incorporated herein by reference) |
| 10.2(g)# | Puma Biotechnology, Inc. 2017 Employment Inducement Incentive Award Plan (filed as Exhibit 99.1 to the Company's Registration Statement on Form S-8 filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.2(h)# | First Amendment to Puma Biotechnology, Inc. 2017 Employment Inducement Incentive Award Plan (filed as Exhibit 99.2 to the Company's Registration Statement on Form S-8 filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.2(i)# | Second Amendment to Puma Biotechnology, Inc. 2017 Incentive Award Plan (filed as Exhibit 99.12 to the Company's Current Report on Form S-8 filed with the SEC on September 16, 2021, and incorporated herein by reference) |
| 10.2(j)# | Form of Stock Option Grant Notice and Stock Option Agreement, issued pursuant to the 2011 Incentive Award Plan (filed as Exhibit 10.5 to the Company's Annual Report on Form 10-K filed with the SEC on March 29, 2012 and incorporated herein by reference) |
| 10.2(k)# | Form of Chief Executive Officer Stock Option Grant Notice and Stock Option Agreement, issued pursuant to the 2011 Incentive Award Plan (filed as Exhibit 10.6 to the Company's Annual Report on Form 10-K filed with the SEC on March 29, 2012 and incorporated herein by reference) |
| 10.2(l)# | Form of Performance Share Award Agreement, issued pursuant to the 2011 Incentive Award Plan (filed as Exhibit 10.2(d) to the Company's Annual Report on Form 10-K filed with the SEC on March 3, 2014 and incorporated herein by reference) |
| 10.2(m)# | Form of Restricted Stock Unit Award Agreement, issued pursuant to the 2011 Incentive Award Plan (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on October 17, 2016 and incorporated herein by reference) |
| 10.2(n)# | Form of Stock Option Grant Notice and Stock Option Agreement, issued pursuant to the 2017 Employment Inducement Incentive Award Plan (filed as Exhibit 10.2(k) to the Company's Annual Report on Form 10-K filed with the SEC on March 1, 2019 and incorporated herein by reference) |
| 10.3(a) | Office Lease by and between the Company and CA - 10880 Wilshire Limited Partnership, executed on December 7, 2011 (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on December 13, 2011 and incorporated herein by reference) |

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| 10.3(b) | First Amendment to the Office Lease, dated as of November 28, 2012, by and between the Company and CA - 10880 Wilshire Limited Partnership (filed as Exhibit 10.13(b) to the Company's Annual Report on Form 10-K filed with the SEC on April 1, 2013 and incorporated herein by reference) |
| 10.3(c) | Second Amendment to the Office Lease, dated as of December 3, 2013, by and between the Company and CA - 10880 Wilshire Limited Partnership (filed as Exhibit 10.6(c) to the Company's Annual Report on Form 10-K filed with the SEC on March 3, 2014 and incorporated herein by reference) |
| 10.3(d) | Third Amendment to the Office Lease, dated as of March 18, 2014, by and between the Company and CA - 10880 Wilshire Limited Partnership (filed as Exhibit 10.5(d) to the Company's Annual Report on Form 10-K filed with the SEC on March 2, 2015 and incorporated herein by reference) |
| 10.3(e) | Fourth Amendment to the Office Lease, dated as of July 31, 2015, by and between the Company and CA - 10880 Wilshire Limited Partnership (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed with the SEC on November 9, 2015 and incorporated herein by reference) |
| 10.4# | Employment Agreement, dated January 19, 2012, by and between the Company and Alan H. Auerbach (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on January 24, 2012 and incorporated herein by reference) |
| 10.5(a) | Office Lease by and between DWF III Gateway, LLC and the Company, executed June 7, 2012 (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on June 13, 2012 and incorporated herein by reference) |
| 10.5(b) | First Amendment to Lease, dated as of May 19, 2014, by and between DWF III Gateway, LLC and Puma Biotechnology, Inc. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on May 23, 2014 and incorporated herein by reference) |
| 10.5(c) | Second Amendment to Lease, dated as of June 10, 2014, by and between DWF III Gateway, LLC and Puma Biotechnology, Inc. (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed with the SEC on August 10, 2015 and incorporated herein by reference) |
| 10.5(d) | Third Amendment to Lease, dated as of July 21, 2015, by and between PR 707 Gateway, LLC (as successor in interest to DWF III Gateway, LLC) and the Company (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed with the SEC on November 9, 2015 and incorporated herein by reference) |
| 10.6# | Letter Agreement, dated May 2, 2012, between the Company and Richard P. Bryce (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on June 26, 2012 and incorporated herein by reference) |
| 10.7# | Form of Indemnification Agreement (filed as Exhibit 10.17 to the Company's Registration Statement on Form S-1/A filed with the SEC on October 15, 2012 and incorporated herein by reference) |
| 10.8# | Amended Non-Employee Director Compensation Program (filed as Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 7, 2020 and incorporated herein by reference) |
| 10.9(a)* | License Agreement, dated November 20, 2017, by and between the Company and Specialised Therapeutics Asia Pte Ltd. (filed as Exhibit 10.13 to the Company's Annual Report on Form 10-K filed with the SEC on March 9, 2018 and incorporated herein by reference) |
| 10.9(b)* | Amendment No. 1, dated April 20, 2018, to the License Agreement by and between the Company and Specialised Therapeutics Asia Pte Ltd. (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed with the SEC on August 9, 2018 and incorporated herein by reference) |
| 10.10# | Letter Agreement, dated December 8, 2017, between the Company and Douglas Hunt (filed as Exhibit 10.15 to the Company's Annual Report on Form 10-K filed with the SEC on March 9, 2018 and incorporated herein by reference) |

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| 10.11(a)* | Collaboration and License Agreement, dated January 30, 2018, between the Company and CANbridge Biomed Limited (as successor in interest to CANbridgepharma Limited) (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 10, 2018 and incorporated herein by reference) |
| 10.11(b)* | Side Letter Agreement, dated November 19, 2018, between the Company and CANbridge Biomed Limited (as successor in interest to CANbridgepharma Limited) (filed as Exhibit 10.15(b) to the Company's Annual Report on Form 10-K filed with the SEC on March 1, 2019 and incorporated herein by reference) |
| 10.11(c)** | Termination Agreement, dated February 24, 2021, by and between the Company and CANbridge BIOMED Limited (filed as Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 6, 2021 and incorporated herein by reference) |
| 10.12* | License Agreement, dated March 30, 2018, between the Company and Pint Pharma International SA (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 10, 2018 and incorporated herein by reference) |
| 10.13* | Supply Agreement, dated April 20, 2018, by and between the Company and Specialised Therapeutics Asia Pte. Ltd. (filed as Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed with the SEC on August 9, 2018 and incorporated herein by reference) |
| 10.14# | Letter Agreement, dated September 28, 2018, between the Company and Maximo F. Nougues (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K filed with the SEC on November 9, 2018 and incorporated herein by reference) |
| 10.15(a)* | License Agreement, dated January 9, 2019, by and between the Company and Knight Therapeutics Inc. (filed as Exhibit 10.19 to the Company's Annual Report on Form 10-K filed with the SEC on March 1, 2019 and incorporated herein by reference) |
| 10.15(b)** | Amendment to the License Agreement, dated December 18, 2019, by and between the Company and Knight Therapeutics, Inc. (filed as Exhibit 10.17(b) to the Company's Annual Report on Form 10-K filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.16(a)** | License Agreement, dated March 29, 2019, by and between the Company and Pierre Fabre Medicament SAS (filed as Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 10, 2019 and incorporated herein by reference) |
| 10.16(b)** | First Amendment to the License Agreement, dated September 17, 2019, by and between the Company and Pierre Fabre Medicament SAS (filed as Exhibit 10.18(b) to the Company's Annual Report on Form 10-K filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.16(c)** | Second Amendment to the License Agreement, dated November 25, 2019, by and between the Company and Pierre Fabre Medicament SAS (filed as Exhibit 10.18(c) to the Company's Annual Report on Form 10-K filed with the SEC on February 28, 2020 and incorporated herein by reference) |
| 10.16(d)** | Amendment No. 3 to the License Agreement, dated February 24, 2021, by and between the Company and Pierre Fabre Medicament SAS (filed as Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed with the SEC on May 6, 2021 and incorporated herein by reference) |
| 10.17# | Letter Agreement, dated February 13, 2020, by and between the Company and Jeff J. Ludwig (filed as Exhibit 10.19 to the Company's Annual Report on Form 10-K filed with the SEC on March 1, 2021 and incorporated herein by reference) |
| 10.18(a)** | Note Purchase Agreement, dated July 23, 2021, by and between the Company and Athyrium Opportunities IV Co-Invest 1 LP, as Administrative Agent (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed with the SEC on November 4, 2021 and incorporated herein by reference) |

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|---|---|
| 10.18(b)+** | First Amendment to Note Purchase Agreement, dated February 8, 2022, by and between the Company and Athyrium Opportunities IV CO-Invest 1 LP, as Administrative Agent |
| 10.19 | Open Market Sale Agreement[SM], dated November 4, 2021, by and between the Company and Jeffries LLC (filed as Exhibit 1.1 to the Company's Current Report on Form 8-K filed with the SEC on November 4, 2021 and incorporated herein by reference) |
| 21.1+ | Subsidiaries |
| 23.1+ | Consent of KPMG LLP |
| 24.1+ | Power of Attorney (included on signature page) |
| 31.1+ | Certification of Principal Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 |
| 31.2+ | Certification of Principal Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 |
| 32.1++ | Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 |
| 32.2++ | Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 |
| 101.INS+ | Inline XBRL Instance Document |
| 101.SCH+ | Inline XBRL Taxonomy Extension Schema Document |
| 101.CAL+ | Inline XBRL Taxonomy Extension Calculation Linkbase Document |
| 101.DEF+ | Inline XBRL Taxonomy Extension Definition Linkbase Document |
| 101.LAB+ | Inline XBRL Taxonomy Extension Label Linkbase Document |
| 101.PRE+ | Inline XBRL Taxonomy Extension Linkbase Document |
| 104+ | Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101) |
| + | Filed herewith |
| ++ | Furnished herewith |
| * | Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment pursuant to Rule 24b-2 under the Securities Exchange Act of 1934. |
| ** | Portions of this exhibit (indicated by asterisks) have been omitted pursuant to Regulation S-K, Item 601(b)(10). Such omitted information is not material and would likely cause competitive harm to the registrant if publicly disclosed. Additionally, certain schedules and attachments to certain of these exhibits have been omitted pursuant to Regulation S-K, Item 601(a)(5). |
| # | Management contract or compensatory plan or arrangement. |

**Signatures**

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on March 3, 2022.

PUMA BIOTECHNOLOGY, INC.

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

**Power of Attorney**

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

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

| Signature | Date |
|---|---|
| /s/ Alan H. Auerbach<br>Alan H. Auerbach | March 3, 2022 |
| /s/ Maximo Nougues<br>Maximo Nougues | March 3, 2022 |
| /s/ Allison Dorval<br>Allison Dorval | March 3, 2022 |
| /s/ Michael P. Miller<br>Michael P. Miller | March 3, 2022 |
| /s/ Jay M. Moyes<br>Jay M. Moyes | March 3, 2022 |
| /s/ Adrian M. Senderowicz<br>Adrian M. Senderowicz | March 3, 2022 |
| /s/ Brian M. Stuglik<br>Brian M. Stuglik | March 3, 2022 |
| /s/ Troy E. Wilson<br>Troy E. Wilson | March 3, 2022 |

**PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARIES**
**INDEX TO CONSOLIDATED FINANCIAL STATEMENTS**

## Report of Independent Registered Public Accounting Firm

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

*Opinions on the* Consolidated Financial Statements *and Internal Control Over Financial Reporting*

We have audited the accompanying consolidated balance sheets of Puma Biotechnology, Inc. and subsidiaries (the Company) as of December 31, 2021 and December 31, 2020, the related consolidated statements of operations, comprehensive loss, stockholders' deficit, and cash flows for each of the years in the three-year period ended December 31, 2021, and the related notes (collectively, the consolidated financial statements). We also have audited the Company's internal control over financial reporting as of December 31, 2021, 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 consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and December 31, 2020, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021 based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

*Basis for Opinions*

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's consolidated financial statements and an opinion on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (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 audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

*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.

*Critical Audit Matter*

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Estimate of certain variable consideration related to product revenue, net

As discussed in Note 2 to the consolidated financial statements, the Company recognizes product revenue, net that includes estimates of variable consideration. For the year ended December 31, 2021, the Company recorded product revenue, net of $189.1 million. The components of variable consideration include trade discounts and allowances, product returns, provider chargebacks and discounts, government rebates, payor rebates, and other incentives. These estimates take into consideration a range of possible outcomes that are probability-weighted in accordance with the expected value method in Accounting Standards Codification (ASC) 606, Revenue from Contracts with Customers. The range of possible outcomes is driven by relevant factors such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns.

We identified the estimate of variable consideration for provider chargebacks and government rebates, including consideration of the constraint on variable consideration, related to product revenue, net as a critical audit matter. Evaluating the key assumptions of forecasted patient buying and payment patterns underlying the estimate for provider chargebacks and government rebates involved especially challenging auditor judgment due to their measurement uncertainty. We performed a sensitivity analysis in order to identify the key assumptions used to estimate the Company's variable consideration. These key assumptions relate to estimating which of the Company's revenue transactions will ultimately be subject to a related provider chargeback or government rebate.

The following are the primary procedures we performed to address this critical audit matter. We evaluated the design and tested the operating effectiveness of certain internal controls related to the development of the key assumptions used to determine variable consideration for provider chargebacks and government rebates, including consideration of the constraint on variable consideration. We evaluated the forecasted patient buying and payment patterns used to determine the provider chargebacks and government rebates by comparing them to the Company's historical data, statutory information, and executed third-party contracts. We assessed the Company's assumed patient buying and payment patterns by (1) independently recalculating historical actual patient buying and payment pattern rates based on historical actual claim data, and (2) comparing current period forecasts to historical actual rates. We evaluated the Company's ability to accurately estimate provider chargebacks and government rebates, including consideration of the constraint on variable consideration, by comparing historically recorded accruals to the actual amount that was ultimately paid by the Company.

/s/ KPMG LLP

We have served as the Company's auditor since 2017.

Los Angeles, California
March 3, 2022

**PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARIES**
**CONSOLIDATED BALANCE SHEETS**
**(in thousands, except share and per share data)**

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| ***ASSETS*** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 63,131 | $ 85,293 |
| Marketable securities | 18,975 | 8,096 |
| Accounts receivable, net of allowance for credit loss of $0 and $1,000 | 32,526 | 25,543 |
| Inventory, net | 7,109 | 3,454 |
| Prepaid expenses, current | 8,984 | 11,262 |
| Restricted cash, current | 8,850 | 8,850 |
| Other current assets | 447 | 3,641 |
| Total current assets | 140,022 | 146,139 |
| Lease right-of-use assets, net | 14,017 | 16,404 |
| Property and equipment, net | 1,756 | 2,481 |
| Intangible assets, net | 66,125 | 74,140 |
| Restricted cash, long-term | 3,311 | 3,311 |
| Prepaid expenses and other, long-term | 1,354 | 1,745 |
| Total assets | $ 226,585 | $ 244,220 |
| ***LIABILITIES AND STOCKHOLDERS' DEFICIT*** | | |
| Current liabilities: | | |
| Accounts payable | $ 11,174 | $ 12,076 |
| Accrued expenses, current | 92,575 | 61,325 |
| Accrued in-licensed rights, current | — | 20,993 |
| Post-marketing commitment liability, current | 2,263 | 2,481 |
| Lease liabilities, current | 3,574 | 3,094 |
| Current portion of long-term debt | — | 14,286 |
| Total current liabilities | 109,586 | 114,255 |
| Accrued expenses, long-term | 915 | 25,963 |
| Lease liabilities, long-term | 15,975 | 19,549 |
| Post-marketing commitment liability, long-term | 5,463 | 6,379 |
| Long-term debt, net | 97,092 | 84,025 |
| Total liabilities | 229,031 | 250,171 |
| Commitments and contingencies (Note 14) | | |
| Stockholders' deficit: | | |
| Common stock - $.0001 par value per share; 100,000,000 shares authorized; 41,175,507 shares issued and outstanding at December 31, 2021 and 40,086,387 issued and outstanding at December 31, 2020 | 4 | 4 |
| Additional paid-in capital | 1,364,309 | 1,331,676 |
| Accumulated other comprehensive income | (2) | — |
| Accumulated deficit | (1,366,757) | (1,337,631) |
| Total stockholders' deficit | (2,446) | (5,951) |
| Total liabilities and stockholders' deficit | $ 226,585 | $ 244,220 |

See Accompanying Notes to the Consolidated Financial Statements

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

| | For the Year Ended December 31, | | |
|---|---|---|---|
| | **2021** | **2020** | **2019** |
| Revenue: | | | |
| Product revenue, net | $ 189,064 | $ 196,728 | $ 211,619 |
| License revenue | 51,750 | 22,700 | 60,250 |
| Royalty revenue | 12,341 | 5,682 | 391 |
| Total revenue | 253,155 | 225,110 | 272,260 |
| Operating costs and expenses: | | | |
| Cost of sales | 63,701 | 39,374 | 36,815 |
| Selling, general and administrative | 116,294 | 118,488 | 141,639 |
| Research and development | 71,870 | 97,650 | 132,851 |
| Total operating costs and expenses | 251,865 | 255,512 | 311,305 |
| Income (1oss) from operations | 1,290 | (30,402) | (39,045) |
| Other income (expenses): | | | |
| Interest income | 160 | 489 | 2,847 |
| Interest expense | (12,807) | (14,046) | (15,019) |
| Legal verdict expense | (9,591) | (16,196) | (16,350) |
| Loss on debt extinguishment | (8,146) | — | (8,103) |
| Other income | 292 | 367 | 128 |
| Total other expenses | (30,092) | (29,386) | (36,497) |
| Loss before income taxes | $ (28,802) | (59,788) | (75,542) |
| Income tax expense | (324) | (207) | (53) |
| Net loss | $ (29,126) | $ (59,995) | $ (75,595) |
| Net loss applicable to common stockholders | $ (29,126) | $ (59,995) | $ (75,595) |
| Net loss per share of common stock—basic and diluted | $ (0.72) | $ (1.52) | $ (1.95) |
| Weighted-average shares of common stock outstanding—basic and diluted | 40,638,852 | 39,576,107 | 38,768,653 |

See Accompanying Notes to the Consolidated Financial Statements

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

| | For the Year Ended December 31, | | |
|---|---|---|---|
| | **2021** | **2020** | **2019** |
| Net loss | $ (29,126) | $ (59,995) | $ (75,595) |
| Other comprehensive (loss) income: | | | |
| Unrealized (loss) gain on available-for-sale securities, net of tax of $0, $0, and $0 | (2) | (65) | 72 |
| Reclassifications of gain on available-for-sale securities, included in "Other income (expenses)," net of tax of $0, $0, and $0 | — | 3 | 2 |
| Comprehensive loss | $ (29,128) | $ (60,057) | $ (75,521) |

See Accompanying Notes to the Consolidated Financial Statements

**PUMA BIOTECHNOLOGY, INC. AND SUBSIDIARIES**
**CONSOLIDATED STATEMENTS OF STOCKHOLDERS' DEFICIT**
**(in thousands, except share and per share data)**

| | Common Stock | | Additional Paid-in Capital | Accumulated Other Comprehensive Income (Loss) | Accumulated Deficit | Total |
|---|---|---|---|---|---|---|
| | Shares | Amount | | | | |
| Balance at December 31, 2018 | 38,325,037 | $ 4 | $ 1,236,355 | $ (12) | $ (1,202,041) | $ 34,306 |
| Stock-based compensation | — | — | 57,327 | — | — | 57,327 |
| Shares issued or restricted stock units vested under employee stock plans | 878,267 | — | 1,351 | — | — | 1,351 |
| Reclassification of gain on available-for-sale securities | — | — | — | 2 | — | 2 |
| Unrealized gain on available-for- sale securities | — | — | — | 72 | — | 72 |
| Net loss | — | — | — | — | (75,595) | (75,595) |
| Balance at December 31, 2019 | 39,203,304 | 4 | 1,295,033 | 62 | (1,277,636) | 17,463 |
| Stock-based compensation | — | — | 36,575 | — | — | 36,575 |
| Shares issued or restricted stock units vested under employee stock plans | 883,083 | — | 68 | — | — | 68 |
| Reclassification of gain on available-for-sale securities | — | — | — | 3 | — | 3 |
| Unrealized gain on available-for- sale securities | — | — | — | (65) | — | (65) |
| Net loss | — | — | — | — | (59,995) | (59,995) |
| Balance at December 31, 2020 | 40,086,387 | 4 | 1,331,676 | — | (1,337,631) | (5,951) |
| Stock-based compensation | — | — | 32,633 | — | — | 32,633 |
| Shares issued or restricted stock units vested under employee stock plans | 1,089,120 | — | — | — | — | — |
| Unrealized loss on available-for-sale securities | — | — | — | (2) | — | (2) |
| Net loss | — | — | — | — | (29,126) | (29,126) |
| Balance at December 31, 2021 | 41,175,507 | $ 4 | $ 1,364,309 | $ (2) | $ (1,366,757) | $ (2,446) |

See Accompanying Notes to the Consolidated Financial Statements

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

| | For the Year Ended December 31, | | |
|---|---|---|---|
| | 2021 | 2020 | 2019 |
| Operating activities: | | | |
| Net loss | $ (29,126) | $ (59,995) | $ (75,595) |
| Adjustments to reconcile net loss to net cash provided by (used in) operating activities: | | | |
| Depreciation and amortization | 10,598 | 10,033 | 8,077 |
| Stock-based compensation | 32,633 | 36,575 | 57,327 |
| Provision for credit loss expense (recovery) | (1,000) | 1,000 | — |
| Disposal of property and equipment | 1 | — | 54 |
| Loss on impairment of asset | — | — | 1,183 |
| Loss on debt extinguishment | 8,146 | — | 8,047 |
| Changes in operating assets and liabilities: | | | |
| Accounts receivable, net | (5,983) | 2,353 | (8,123) |
| Inventory, net | (3,655) | (284) | (545) |
| Prepaid expenses and other | 2,669 | 2,207 | 414 |
| Other current assets | 3,194 | (3,120) | 1,464 |
| Accounts payable | (902) | (7,107) | (1,526) |
| Accrued expenses and other | 5,209 | 19,251 | 22,599 |
| Post-marketing commitment liability | (1,134) | (140) | 9,000 |
| Net cash provided by operating activities | 20,650 | 773 | 22,376 |
| Investing activities: | | | |
| Purchase of property and equipment | — | (46) | (306) |
| Purchase of available-for-sale securities | (38,073) | (29,826) | (127,198) |
| Sale of available-for-sale securities | — | — | 28,135 |
| Maturity of available-for-sale securities | 27,192 | 73,275 | 104,532 |
| Purchase of intangible assets | — | (10,000) | — |
| Net cash provided by (used in) investing activities | (10,881) | 33,403 | 5,163 |
| Financing activities: | | | |
| Net proceeds from shares issued under employee stock plans | — | 68 | 1,351 |
| Proceeds from debt | 98,500 | 8,444 | 25,000 |
| Payment of debt | (100,000) | (8,444) | (80,000) |
| Payment of prepayment costs, end of loan payment and other extinguishment costs | (8,521) | — | (7,793) |
| Payment of debt issuance costs | (1,910) | — | (5,625) |
| Installment payment for purchase of intangible asset | (20,000) | (10,000) | — |
| Net cash used in financing activities | (31,931) | (9,932) | (67,067) |
| Net increase (decrease) in cash, cash equivalents and restricted cash | (22,162) | 24,244 | (39,528) |
| Cash, cash equivalents and restricted cash, beginning of period | 97,454 | 73,210 | 112,738 |
| Cash, cash equivalents and restricted cash, end of period | $ 75,292 | $ 97,454 | $ 73,210 |
| | | | |
| Supplemental disclosures of non-cash investing and financing activities: | | | |
| Intangibles in accrued expenses | $ — | $ 20,000 | $ — |
| Property and equipment purchases in accounts payable | $ — | $ — | $ 25 |
| | | | |
| Supplemental disclosure of cash flow information: | | | |
| Interest paid | $ 10,342 | $ 9,703 | $ 11,739 |
| Income taxes paid | $ 324 | $ 207 | $ 53 |

See Accompanying Notes to the Consolidated Financial Statements

**Note 1—Business and Basis of Presentation**

Puma Biotechnology, Inc. (the "Company") is a biopharmaceutical company based in Los Angeles, California with a focus on the development and commercialization of innovative products to enhance cancer care. The Company in-licenses from Pfizer Inc. ("Pfizer") the global development and commercialization rights to PB272 (neratinib (oral)), PB272 (neratinib (intravenous)) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor that blocks signal transduction through the epidermal growth factor receptors HER1, HER2 and HER4. Currently, the Company is primarily focused on the development and commercialization of the oral version of neratinib, and its most advanced drug candidates are directed at the treatment of HER2-positive breast cancer and HER2 mutated cancers. The Company believes neratinib has clinical application in the treatment of several other cancers as well, including other tumor types that over-express or have a mutation in HER2, such as breast cancer, cervical cancer, lung cancer or other solid tumors.

The Company has two subsidiaries, Puma Biotechnology Ltd., a United Kingdom company, and Puma Biotechnology, B.V., a Netherlands company. These subsidiaries were established for the purpose of legal representation in the United Kingdom and the European Union. The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All significant intercompany accounts and transactions have been eliminated.

The accompanying consolidated financial statements of the Company and its subsidiaries have been prepared in accordance with U.S. generally accepted accounting principles ("US GAAP").

The Company has incurred significant operating losses since its inception. The Company believes that it will continue to incur net losses and may incur negative net cash flows from operating activities through the drug development process and global commercialization. In 2017, the Company received U.S. Food and Drug Administration ("FDA") approval for its first product, NERLYNX® (neratinib)("NERLYNX"), formerly known as PB272 (neratinib, oral), for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy. Following FDA approval in July 2017, NERLYNX became available by prescription in the United States, and the Company commenced commercialization.

In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

In 2018, the European Commission ("EC") granted marketing authorization for NERLYNX in the European Union ("EU") for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy.

The Company is required to make substantial payments to Pfizer upon the achievement of certain milestones and has contractual obligations for clinical trial contracts.

The Company has entered into other exclusive sub-license agreements with various parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved, in many regions outside the United States, including Europe (excluding Russia and Ukraine), Australia, Canada, China, Southeast Asia, Israel, South Korea, and various countries and territories in Central and South America. The Company plans to continue to pursue commercialization of NERLYNX in other countries outside the United States, if approved.

The Company has reported a net loss of approximately $29.1 million and cash flows from operations of approximately $20.7 million for the year ended December 31, 2021. The Company’s commercialization, research and development or marketing efforts may require funding in addition to the cash and cash equivalents and marketable securities totaling approximately $82.1 million at December 31, 2021. The Company believes that its existing cash and cash equivalents and marketable securities as of December 31, 2021 and proceeds that will become available to the Company through product sales and sub-license payments are sufficient to satisfy its operating cash needs for at least one year after the filing of the Annual Report on Form 10-K in which these financial statements are included. The Company continues to remain dependent on its ability to obtain sufficient funding to sustain operations and continue to successfully commercialize neratinib in the United States. While the Company has been successful in raising capital in the past, there

can be no assurance that it will be able to do so in the future. The Company's ability to obtain funding may be adversely impacted by uncertain market conditions, including the global COVID-19 pandemic, the Company's success in commercializing neratinib, unfavorable decisions of regulatory authorities or adverse clinical trial results. The outcome of these matters cannot be predicted at this time. Additionally, the terms of the Company's note purchase agreement place restrictions on the Company's ability to operate the business and on the Company's financial flexibility, and the Company may be unable to achieve the revenue necessary to satisfy the minimum revenue and cash balance covenants as specified in the agreement.

Since its inception through December 31, 2021, the Company's financing has primarily been proceeds from product, royalty, and license revenue, public offerings of its common stock, private equity placements, and various debt instruments.

**Note 2—Significant Accounting Policies**

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

**Principles of Consolidation**

The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

**Reclassifications**

In preparing the 2021 consolidated statement of cash flows, the Company determined that $10.0 million paid for the purchase of intangible assets was incorrectly presented as cash used in investing activities for the year ended December 31, 2020. This error was not considered material to the Company's consolidated financial statements and the payment has been correctly presented as cash used in financing activities in the accompanying comparative financial statements.

**Segment Reporting**

Management has determined that the Company operates in one business segment, which is the development and commercialization of innovative products to enhance cancer care.

**Use of Estimates**

The preparation of consolidated financial statements in conformity with US GAAP requires management to make estimates and assumptions that affect reported amounts of assets and liabilities, and disclosure of contingent assets and liabilities at the date of the balance sheet, and reported amounts of revenues and expenses for the period presented. Accordingly, actual results could differ from those estimates.

Significant estimates include estimates for variable consideration for which reserves were established. These estimates are included in the calculation of net revenues and 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 the Company and its customers, payors, and other indirect customers relating to the Company's sale of its products. Other significant estimates also include those related to legal and other expense accruals.

**Net Loss per Share of Common Stock**

Basic net loss per share of common stock is computed by dividing net loss applicable to common stockholders by the weighted average number of shares of common stock outstanding during the periods presented, as required by ASC 260 Earnings per Share. For purposes of calculating diluted loss per share of common stock, the denominator includes both the weighted average number of shares of common stock outstanding and the number of dilutive common stock equivalents, such as stock options, restricted stock units ("RSUs") and warrants. A common stock equivalent is not included in the denominator when calculating diluted earnings per common share if the effect of such common stock equivalent would be anti-dilutive. The following potentially dilutive outstanding common stock equivalents were excluded from diluted net loss per share because of their anti-dilutive effect:

| | For the Years Ended December 31, | | |
|---|---|---|---|
| | 2021 | 2020 | 2019 |
| Options outstanding | 4,595,247 | 5,009,342 | 5,042,325 |
| Warrant outstanding | 2,116,250 | 2,116,250 | 2,116,250 |
| Unvested restricted stock units | 1,399,317 | 1,854,205 | 1,991,125 |
| Totals | 8,110,814 | 8,979,797 | 9,149,700 |

**Revenue Recognition**

Under ASC Topic 606, *Revenue from Contracts with Customers* ("ASC 606") the Company 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. The Company had no contracts with customers until the FDA approved NERLYNX on July 17, 2017. Subsequent to receiving FDA approval, the Company entered into a limited number of arrangements with specialty pharmacies and specialty distributors in the United States to distribute NERLYNX. These arrangements are the Company's initial contracts with customers. The Company has determined that these sales channels with customers are similar.

***Product Revenue, Net***

The Company sells NERLYNX to a limited number of specialty pharmacies and specialty distributors in the United States. These customers subsequently resell the Company's products to patients and certain medical centers or hospitals. In addition to distribution agreements with these customers, the Company enters into arrangements with health care providers and payors that provide for government mandated and/or privately negotiated rebates, chargebacks and discounts with respect to the purchase of the Company's products.

The Company recognizes revenue on product sales when the specialty pharmacy or specialty distributor, as applicable, obtains control of the Company's product, which occurs at a point in time (upon delivery). Product revenue is recorded net of applicable reserves for variable consideration, including discounts and allowances. The Company's payment terms range between 10 and 68 days.

Shipping and handling costs for product shipments occur prior to the customer obtaining control of the goods and are recorded in cost of sales.

If taxes should be collected from customers relating to product sales and remitted to governmental authorities, they will be excluded from revenue. The Company expenses incremental costs of obtaining a contract when incurred, if the expected amortization period of the asset that the Company would have recognized is one year or less. However, no such costs were incurred during the year ended December 31, 2021.

For the period ended December 31, 2021, two major customers represented approximately 31% and 22%, respectively, of the Company's total product revenue. For the period ended December 31, 2020, two major customers accounted for approximately 33% and 21%, respectively, of the Company's total product revenue. For the period ended December 31, 2019, two major customers accounted for approximately 34% and 22%, respectively, of the Company's total product revenue.

***Reserves for Variable Consideration***

Revenue from product sales is 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 the Company and its customers, payors, and other indirect customers relating to the Company's sale of its products. These reserves, as detailed below, are based on the related sales, and are classified as reductions of accounts receivable, net when the right of offset exists in accordance with ASU 2013-1, *Balance Sheet (Topic 210): Clarifying the Scope of Disclosures about Offsetting Assets and Liabilities*, or as a current liability. These estimates take into consideration a range of possible outcomes that are probability-weighted in accordance with the expected value method in ASC 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 the Company's 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 that 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. The Company's analyses also contemplated application of the constraint in accordance with the guidance, under which it determined a significant reversal of revenue would not occur in a future period for the estimates detailed below as of December 31, 2021 and, therefore, the transaction price was not reduced further during the year ended December 31, 2021. Actual amounts of consideration ultimately received may differ from the Company's estimates. If actual results in the future vary from the Company's estimates, the Company will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

***Trade Discounts and Allowances***

The Company generally provides customers with discounts, which include incentive fees that are explicitly stated in the Company's contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized. The reserve for discounts is established in the same period that the related revenue is recognized, together with reductions to accounts receivables, net on the consolidated balance sheets. In addition, the Company compensates its customers for sales order management, data, and distribution services. The Company has determined such services received to date are not distinct from the Company's sale of products to its customers and, therefore, these payments have been recorded as a reduction of revenue within the statement of operations.

***Product Returns***

Consistent with industry practice, the Company offers the specialty pharmacies and specialty distributors that are its customers limited product return rights for damaged and expiring product, provided it is within a specified period around the product expiration date as set forth in the applicable individual distribution agreement. The Company estimates the amount of its product sales that may be returned by its customers and records this estimate as a reduction of revenue in the period the related product revenue is recognized, as well as a reduction to accounts receivables, net on the consolidated balance sheets. The Company currently estimates product returns using its own sales information, including its visibility into the inventory remaining in the distribution channel. The Company has an insignificant amount of returns to date and believes that returns of its 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 its customers who directly purchase the product from the Company. Customers charge the Company for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. The reserve for chargebacks is established in the same period that the related revenue is recognized, resulting in a reduction of product revenue and a reduction to accounts receivable, net on the consolidated balance sheets. Chargeback amounts are generally determined at the time of resale to the qualified healthcare provider by customers, and the Company generally issues credits for such amounts within a few weeks of the customer's notification to the Company of the resale. Chargebacks consist of credits the Company expects to issue for units that remain in the distribution channel at each reporting period end that the Company expects will be sold to qualified healthcare providers and chargebacks that customers have claimed, but for which the Company has not yet issued a payment.

***Government Rebates***

The Company is 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 on the consolidated balance sheets. The Company's 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 estimates of 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***

The Company contracts with certain private payor organizations, primarily insurance companies and pharmacy benefit managers, for the payment of rebates with respect to utilization of its products. The Company estimates these rebates and records such estimates in the same period the related revenue is recognized, resulting in a reduction of product revenue, net and the establishment of a current liability, which is included in accrued expenses on the consolidated balance sheets.

***Other Incentives***

Other incentives the Company offers 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 the Company expects 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 on the consolidated balance sheets.

***License Revenue***

The Company also recognizes license revenue under certain of the Company's sub-license agreements that are within the scope of ASC 606. The terms of these agreements may contain multiple performance obligations, which may include licenses and research and development activities. The Company evaluates these agreements under ASC 606 to determine the distinct performance obligations. Non-refundable, upfront fees that are not contingent on any future performance and require no consequential continuing involvement by the Company, are recognized as revenue when the license term commences and the licensed data, technology or product is delivered. The Company defers recognition of non-refundable upfront license fees if the performance obligations are not satisfied. The Company's payment terms range between the execution date of the sub-license agreement and 45 days.

Prior to recognizing revenue, the Company makes estimates of the transaction price, including variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved.

If there are multiple distinct performance obligations, the Company allocates the transaction price to each distinct performance obligation based on its relative standalone selling price. The standalone selling price is generally determined based on the prices charged to customers or using expected cost-plus margin. Revenue is recognized by measuring the progress toward complete satisfaction of the performance obligations using an input measure.

Since 2018, the Company has entered into sub-license agreements with certain sub-licensees in territories outside of the United States. These sub-licensing agreements grant certain intellectual property rights and set forth various respective obligations with respect to actions such as development, pursuit and maintenance of regulatory approvals, commercialization and supply of NERLYNX in the sub-licensees' respective territories.

License fees under the sub-license agreements include one-time upfront payments when each sub-license agreement was executed and potential additional one-time milestone payments due to the Company upon successful completion of certain performance obligations, such as achieving regulatory approvals or sales target thresholds, and potential double-digit royalties on sales of the licensed product, calculated as a percentage of net sales of the licensed product throughout each sub-licensee's respective territory. As of December 31, 2021, the total potential milestone payments that would be due to the Company upon achievement of all respective performance obligations under the sub-license agreements is approximately $579.8 million. At this time, the Company cannot estimate if or when these milestone-related performance obligations might be achieved.

***Royalty Revenue***

For sub-license agreements that are within the scope of ASC 606, the Company recognizes revenue when the related sales occur in accordance with the sales-based royalty exception under ASC 606-10-55-65. Royalty revenue consists of consideration earned related to international sales of NERLYNX made by the Company's sub-licensees in their respective territories. The Company recognizes royalty revenue when the performance obligations have been satisfied. The Company's payment terms range between 30 and 90 days.

**Legal Contingencies and Expense**

For legal contingencies, the Company accrues a liability for an estimated loss if the potential loss from any claim or legal proceeding is considered probable and the amount can be reasonably estimated. Legal fees and expenses are expensed as incurred based on invoices or estimates provided by legal counsel. The Company periodically evaluates available information, both internal and external, relative to such contingencies and adjusts the accrual as necessary. The Company determines whether a contingency should be disclosed by assessing whether a material loss is deemed reasonably possible. In determining whether a loss should be accrued, the Company evaluates, among other factors, the degree of probability of an unfavorable outcome and the ability to make a reasonable estimate of the amount of the loss (see Note 14-Commitments and Contingencies).

**Royalty Expenses**

Royalties incurred in connection with the Company's license agreement with Pfizer, as disclosed in Note 14-Commitments and Contingencies, are expensed to cost of sales as revenue from product sales is recognized.

**Research and Development Expenses**

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

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

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

**Stock-Based Compensation**

***Stock option awards***

ASC Topic 718, *Compensation-Stock Compensation* ("ASC 718") requires the fair value of all share-based payments to employees and non-employees, including grants of stock options, to be recognized in the statement of operations over the requisite service period. Under ASC 718, employee and non-employee option grants are generally valued at the grant date and those valuations do not change once they have been established. The fair value of each option award is estimated on the grant date using the Black-Scholes Option Pricing Method. As allowed by ASC 718, the Company's estimate of expected volatility is based on its average volatilities using its expected life, or approximately the past six years of publicly traded history. The risk-free rate for periods within the contractual life of the option is based on the U.S. Treasury yield curve in effect at the time of grant valuation. Option forfeitures are estimated when the option is granted to reduce the option expense to be recognized over the life of the award. The estimated forfeiture rate considers historical employee turnover rates stratified into employee pools, actual forfeiture experience and other factors. The option expense is adjusted upon the actual forfeiture of a stock option grant and the Company periodically revises the estimated forfeiture rate in subsequent periods if actual forfeitures differ from those estimates. Due to its limited history of stock option exercises, the Company uses the simplified method to determine the expected life of the option grants. Compensation expense related to modified stock options is measured based on the fair value for the awards as of the modification date. Any incremental compensation expense arising from the excess of the fair value of the awards on the modification date compared to the fair value of the awards immediately before the modification date is recognized at the modification date or ratably over the requisite service period, as appropriate.

***Restricted stock units***

RSUs are valued on the grant date and the fair value of the RSUs is equal to the market price of the Company's common stock on the grant date. The RSU expense is recognized over the requisite service period in the statement of operations. When the requisite service period begins prior to the grant date (because the service inception date occurs prior to the grant date), the Company is required to begin recognizing compensation cost before there is a measurement date (i.e., the grant date). The service inception date is the beginning of the requisite service period. If the service inception date precedes the grant date, accrual of compensation cost for periods before the grant date shall be based on the fair value of the award at the reporting date. In the period in which the grant date occurs, cumulative compensation cost shall be adjusted to reflect the cumulative effect of measuring compensation cost based on fair value at the grant date rather than the fair value previously used at the service inception date (or any subsequent reporting date). RSU forfeitures are estimated when the RSU is granted to reduce the RSU expense to be recognized over the life of the award. The estimated forfeiture rate considers historical employee turnover rates stratified into employee pools, actual forfeiture experience and other factors. The RSU expense is "trued-up" upon the actual forfeiture of a RSU grant and the Company periodically revises the estimated forfeiture rate in subsequent periods if actual forfeitures differ from those estimates. Compensation expense related to modified restricted stock units is measured based on the fair value for the awards as of the modification date. Any incremental compensation expense arising from the excess of the fair value of the awards on the modification date compared to the fair value of the awards immediately before the modification date is recognized at the modification date or ratably over the requisite service period, as appropriate.

***Warrants***

Warrants (see Note 11-Stockholders' (Deficit) Equity for further details) granted to employees and non-employees are normally valued at the fair value of the instrument on the grant date and are recognized in the statement of operations over the requisite service period. When the requisite service period precedes the grant date and a market condition exists in the warrant, the Company values the warrant using the Monte Carlo Simulation Method. When the terms of the warrant become fixed, the Company values the warrant using the Black-Scholes Option Pricing Method. As allowed by ASC 718, the Company's estimate of expected volatility is based on its average volatilities using its past nine years of publicly traded history. The risk-free rate for periods within the contractual life of the warrant is based on the U.S. Treasury yield curve in effect at the time of grant valuation. In determining the value of the warrant until the terms are fixed, the Company factors in the probability of the market condition occurring and several possible scenarios. When the requisite service period precedes the grant date and is deemed to be complete, the Company records the fair value of the warrant at the time of issuance as an equity stock-based compensation transaction. The grant date is determined when all pertinent information, such as exercise price and quantity are known.

**Income Taxes**

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

The standard addresses the determination of whether tax benefits claimed or expected to be claimed on a tax return should be recorded in the consolidated financial statements. Under ASC 740, the Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by the tax authorities, based on the technical merits of the position. The tax benefits recognized in the consolidated financial statements from such a position should be measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate settlement. ASC 740 also provides guidance on de-recognition, classification, interest and penalties on income taxes, accounting in interim periods and requires increased disclosures. As of December 31, 2021, the Company's uncertain tax position includes a reserve for its R&D credits.

**Financial Instruments**

The carrying value of financial instruments, such as cash equivalents, accounts receivable and accounts payable, approximate their fair value because of their short-term nature. The carrying value of long-term debt approximates its fair value as the principal amounts outstanding are subject to variable interest rates that are based on market rates which are regularly reset.

**Cash and Cash Equivalents**

The Company classifies all highly liquid instruments with an original maturity of three months or less as cash equivalents.

**Restricted Cash**

Restricted cash represents cash held at financial institutions that are pledged as collateral for stand-by letters of credit for lease and legal verdict commitments. The lease related letters of credit will lapse at the end of the respective lease terms through 2026. At December 31, 2021 and 2020, the Company had restricted cash in the amount of $12.2 million for both years ended 2021 and 2020.

**Investment Securities**

The Company classifies all investment securities (short-term and long-term) as available-for-sale, as the sale of such securities may be required prior to maturity to implement management's strategies. These securities are carried at fair value, with the unrealized gains and losses, reported as a component of accumulated other comprehensive income (loss) in stockholders' (deficit) equity until realized. Realized gains and losses from the sale of available-for-sale securities, if any, are determined on a specific identification basis. In accordance with ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*, credit losses on available-for-sale securities are reported using an expected loss model and recorded to an allowance. No material credit losses on available-for-sale securities were recognized in the years ending December 31, 2021 Premiums and discounts are amortized or accreted over the life of the related security as an adjustment to yield using the straight-line method. Interest income is recognized when earned.

**Assets Measured at Fair Value on a Recurring Basis**

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

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

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

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

Following are the major categories of assets measured at fair value on a recurring basis as of December 31, 2021 and 2020, using quoted prices in active markets for identical assets (Level 1), significant other observable inputs (Level 2), and significant unobservable inputs (Level 3) (in thousands):

| **December 31, 2021** | **Level 1** | **Level 2** | **Level 3** | **Total** |
|---|---|---|---|---|
| Cash equivalents | $ 50,872 | $ — | $ — | $ 50,872 |
| Commercial paper | — | 14,589 | — | 14,589 |
| Corporate bonds | — | 4,386 | — | 4,386 |
| Totals | $ 50,872 | $ 18,975 | $ — | $ 69,847 |

| **December 31, 2020** | **Level 1** | **Level 2** | **Level 3** | **Total** |
|---|---|---|---|---|
| Cash equivalents | $ 59,919 | $ 11,798 | $ — | $ 71,717 |
| Commercial paper | — | 8,096 | — | 8,096 |
| Totals | $ 59,919 | $ 19,894 | $ — | $ 79,813 |

The Company's investments in commercial paper, corporate bonds and U.S. government securities are exposed to price fluctuations. The fair value measurements for commercial paper, corporate bonds and U.S. government securities are based upon the quoted prices of similar items in active markets multiplied by the number of securities owned.

The following tables summarize the Company's short-term investments (in thousands):

| **December 31, 2021** | **Maturity (in years)** | **Amortized cost** | **Unrealized Gains** | **Unrealized Losses** | **Estimated fair value** |
|---|---|---|---|---|---|
| Cash equivalents | | $ 50,872 | $ — | $ — | $ 50,872 |
| Commercial paper | Less than [1] | 14,590 | — | (1) | 14,589 |
| Corporate bonds | | 4,387 | - | (1) | 4,386 |
| Totals | | $ 69,849 | $ — | $ (2) | $ 69,847 |

| **December 31, 2020** | **Maturity (in years)** | **Amortized cost** | **Unrealized Gains** | **Unrealized Losses** | **Estimated fair value** |
|---|---|---|---|---|---|
| Cash equivalents | | $ 71,717 | $ — | $ — | $ 71,717 |
| Commercial paper | Less than 1 | 8,096 | — | — | 8,096 |
| Totals | | $ 79,813 | $ — | $ — | $ 79,813 |

**Concentration of Risk**

Financial instruments, which potentially subject the Company to concentrations of credit risk, principally consist of cash and cash equivalents, marketable securities, and accounts receivable, net. The Company's cash and cash equivalents and restricted cash in excess of the Federal Deposit Insurance Corporation and the Securities Investor Protection Corporation insured limits at December 31, 2021, were approximately $75.0 million. The Company does not believe it is exposed to any significant credit risk due to the quality nature of the financial instruments in which the money is held. Pursuant to the Company's internal investment policy, investments must be rated A-1/P-1 or better by Standard and Poor's Rating Service and Moody's Investors Service at the time of purchase.

The Company sells its products in the United States primarily through specialty pharmacies and specialty distributors. Therefore, wholesale distributors and large pharmacy chains account for a large portion of its accounts receivables, net and product revenues, net. The creditworthiness of its customers is continuously monitored, and the Company has internal policies regarding customer credit limits. The Company estimates an allowance for credit loss primarily based on the credit worthiness of its customers, historical payment patterns, aging of receivable balances and general economic conditions. The Company recorded credit loss expense of $1.0 million during 2020 and a recovery of credit loss expense in 2021.

The Company's success depends on its ability to successfully commercialize NERLYNX. The Company currently has a single product with limited commercial sales experience, which makes it difficult to evaluate its current business, predict its future prospects and forecast financial performance and growth. The Company has invested a significant portion of its efforts and financial resources in the development and commercialization of the lead product, NERLYNX, and expects NERLYNX to constitute the vast majority of product revenue for the foreseeable future.

The Company relies exclusively on third parties to formulate and manufacture NERLYNX and its drug candidates. The commercialization of NERLYNX and any other drug candidates, if approved, could be stopped, delayed or made less profitable if those third parties fail to provide sufficient quantities of product or fail to do so at acceptable quality levels or prices. The Company has no experience in drug formulation or manufacturing and does not intend to establish its own manufacturing facilities. The Company lacks the resources and expertise to formulate or manufacture NERLYNX and other drug candidates. While the drug candidates were being developed by Pfizer, both the drug substance and drug product were manufactured by third-party contractors. The Company is using the same third-party contractors to manufacture, supply, store and distribute drug supplies for clinical trials and the commercialization of NERLYNX. If the Company is unable to continue its relationships with one or more of these third-party contractors, it could experience delays in the development or commercialization efforts as it locates and qualifies new manufacturers. The Company intends to rely on one or more third-party contractors to manufacture the commercial supply of drugs.

**Inventory**

The Company values its inventories at the lower of cost and estimated net realizable value. The Company determines the cost of its inventories, which includes amounts related to materials and manufacturing overhead, on a first-in, first-out basis. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period, and it writes down any excess and obsolete inventories to their estimated realizable value in the period in which the impairment is first identified. Such impairment charges, should they occur, are recorded within the cost of sales in the consolidated statements of operations. The determination of whether inventory costs will be realizable requires estimates by management. If actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required, which would be recorded as a cost of sales in the consolidated statements of operations.

The Company capitalizes inventory costs associated with the Company's products after regulatory approval, if any, when, based on management's judgment, future commercialization is considered probable and the future economic benefit is expected to be realized. Inventory that can be used in either the production of clinical or commercial product is recorded as research and development expense when selected for use in a clinical trial. Starter kits, provided to patients prior to insurance approval, are expensed by the Company to selling, general and administrative expense as incurred.

The Company's inventory balances are as follows:

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Raw materials | $ 4,569 | $ 1,431 |
| Work-in-process (materials, labor and overhead) | 1,385 | 1,258 |
| Finished goods (materials, labor and overhead) | 1,155 | 765 |
| Total Inventories | $ 7,109 | $ 3,454 |

**Property and Equipment, Net**

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation is computed using the straight-line method over the useful lives of the assets, which is generally three years for computer hardware and software, three years for phone equipment, and seven years for furniture and fixtures. Leasehold improvements are amortized using the straight-line method over the lesser of the useful life or the lease term. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are eliminated from the accounts and any resulting gain or loss is credited or charged to operations. Repairs and maintenance costs are expensed as incurred.

The Company reviews its long-lived assets used in operations for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable, as required by ASC Topic 360, *Property, Plant, and Equipment* ("ASC 360"). The Company performs a recoverability test by comparing the sum of the estimated undiscounted cash flows over the life of the asset to its carrying value on the consolidated balance sheet. If the undiscounted cash flows used in the recoverability test are less than the carrying value, the Company would then determine the fair value of the long-lived asset and recognize an impairment loss for the amount in excess of the carrying value.

**Leases**

ASC Topic 842, *Leases*, as adopted in the first quarter of 2019, requires lessees to recognize most leases on the balance sheet with a corresponding right-of-use asset ("ROU asset"). ROU assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. The assets and lease liabilities are recognized at the lease commencement date based on the estimated present value of fixed lease payments over the lease term. ROU assets are evaluated for impairment using the long-lived assets impairment guidance, as required by ASC 360. A significant indication of impairment of an ROU asset would include a change in the extent or manner in which the asset is being used. The Company must make assumptions which underlie the most significant and subjective estimates in determining whether any impairment exists. Those estimates, and the underlying assumptions, include estimates of future cash flow utilizing market lease rates and determination of fair value. If an ROU asset related to an operating lease is impaired, the carrying value of the ROU asset post-impairment should be amortized on a straight-line basis through the earlier of the end of the useful life of the ROU asset or the end of the lease term. Post impairment, a lessee must calculate the amortization of the ROU asset and interest expense on the lease liability separately, although the sum of the two continues to be presented as a single lease cost. If a lease is planned to be abandoned with no intention of subleasing, the ROU asset should be assessed for impairment.

Leases are classified as financing or operating, which will drive the expense recognition pattern. The Company elects to exclude short-term leases if and when the Company has them. For additional information, see Note 7-Leases.

The Company leases office space and copy machines, all of which are operating leases. Most leases include the option to renew and the exercise of the renewal options is at the Company's sole discretion. Options to extend or terminate a lease are considered in the lease term to the extent that the option is reasonably certain of exercise. The leases do not include options to purchase the leased property. The depreciable life of assets and leasehold improvements is limited by the expected lease term. Covenants imposed by the leases include letters of credit required to be obtained by the lessee.

The incremental borrowing rate ("IBR") represents the rate of interest the Company would expect to pay on a collateralized basis to borrow an amount equal to the lease payments under similar terms. When determinable, the Company uses the rate implicit in the lease to determine the present value of lease payments. As the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at the commencement date in determining the present value of lease payments. The Company's average IBR for existing leases as of December 31, 2021 was 10.9%.

The Company decided to cease the use of a portion of its leased office space in 2019. In connection with the decreased need for the right to use the ROU asset, the Company entered into a sublease for the underlying asset, in which the sublease income is less than the original lease payments, indicating impairment. In performing the recoverability test on the effective date, the undiscounted future estimated cash flows and carrying value were identified for the subleased portion of the leased building, as an individual asset group, defined under ASC 360. A reduction to the carrying value of the ROU asset of approximately $1.2 million was recorded, representing the fair value amount in excess of the carrying value, with a corresponding impairment charge recorded as selling, general and administration expense, in the consolidated statements of operations for the year ended December 31, 2019. There were no indications of impairment or any related charge recorded during the year ended December 31, 2021.

**License Fees and Intangible Assets**

The Company expenses amounts paid to acquire licenses associated with products under development when the ultimate recoverability of the amounts paid is uncertain and the technology has no alternative future use when acquired. Acquisitions of technology licenses are charged to expense or capitalized based upon the asset achieving technological feasibility in accordance with management's assessment regarding the ultimate recoverability of the amounts paid and the potential for alternative future use. The Company has determined that technological feasibility for its product candidates is reached when the requisite regulatory approvals are obtained to make the product available for sale. The Company capitalizes technology licenses upon reaching technological feasibility.

The Company maintains definite-lived intangible assets related to the license agreement with Pfizer. These assets are amortized over their remaining useful lives, which are estimated based on the shorter of the remaining patent life or the estimated useful life of the underlying product. Intangible assets are amortized using the economic consumption method if anticipated future revenues can be reasonably estimated. The straight-line method is used when future revenues cannot be reasonably estimated. Amortization costs are recorded as part of cost of sales.

The Company assesses its intangible assets for impairment if indicators are present or changes in circumstance suggest that impairment may exist. Events that could result in an impairment, or trigger an interim impairment assessment, include the receipt of additional clinical or non-clinical data regarding one of the Company's drug candidates or a potentially competitive drug candidate, changes in the clinical development program for a drug candidate, or new information regarding potential sales for the drug. If impairment indicators are present or changes in circumstance suggest that impairment may exist, the Company performs a recoverability test by comparing the sum of the estimated undiscounted cash flows of each asset group to its carrying value on the consolidated balance sheet. If the undiscounted cash flows used in the recoverability test are less than the carrying value, the Company would determine the fair value of the intangible asset and recognize an impairment loss if the carrying value of the intangible asset exceeds its fair value. In connection with the FDA approval of NERLYNX in July 2017, the Company triggered a one-time milestone payment pursuant to its license agreement with Pfizer. In June 2020, the Company entered into a letter agreement with Pfizer relating to the method of payment associated with a milestone payment under the Company's license agreement with Pfizer (see Note 14-Commitments and Contingencies). The Company capitalized the milestone payments as an intangible asset and is amortizing the asset to cost of sales on a straight-line basis over the estimated useful life of the licensed patent through 2030. The Company recorded amortization expense related to its intangible asset of $8.0 million, $6.3 million, $3.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, estimated future amortization expense related to the Company's intangible asset was approximately $8.0 million for each year starting 2022 through 2029, and $2.0 million for 2030.

**Recently Issued Accounting Standards**

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU-2016-13"). ASU 2016-13 requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For trade accounts receivable, the Company recognizes credit losses based on lifetime expected losses. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. These amendments under ASU 2016-13 are effective for interim and annual fiscal periods beginning after December 15, 2019. The Company adopted ASU 2016-13 as of January 1, 2020, and the adoption did not have a material effect on the Company's current financial position, results of operations or financial statement disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"). As of January 1, 2020, the Company adopted the amendments in ASU 2018-13, which modifies the disclosure requirements on fair value measurements. The removed and modified disclosures were adopted on a retrospective basis and the new disclosures were adopted on a prospective basis. The adoption of ASU 2018-13 did not have a material effect on the Company's current financial position, results of operations or financial statement disclosures.

In December 2019, the FASB issued ASU No 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"), as part of its Simplification Initiative to reduce the cost and complexity in accounting for income taxes. The amendments in ASU 2019-12 remove certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also amends other aspects of the guidance to help simplify and promote consistent application of GAAP. The guidance is effective for interim and annual periods beginning after December 15, 2020, with early adoption permitted. The Company adopted ASU 2019-12 on January 1, 2021 and it did not have a material effect on the Company's current financial position, results of operations or financial statement disclosures.

**Note 3—Accounts Receivable, Net**

Accounts receivable, net consisted of the following (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Trade accounts receivable | $ 29,646 | $ 21,515 |
| License revenue receivable | — | 2,500 |
| Royalty revenue receivable | 2,880 | 2,528 |
| Total accounts receivable | $ 32,526 | $ 26,543 |
| Allowance for credit losses | — | (1,000) |
| Total accounts receivable, net | $ 32,526 | $ 25,543 |

Trade accounts receivable consist entirely of amounts owed from the Company's customers related to product sales. License revenue receivable represents an amount owed from a sub-licensee under a sub-license agreement. Royalty revenue receivable represents amounts owed related to royalty revenue recognized based on the Company's sub-licensees' sales in their respective territories in the years ended December 31, 2021 and 2020.

For all accounts receivable, the Company recognized credit losses based on lifetime expected losses. In determining estimated credit losses, the Company evaluated its historical loss rates, current economic conditions and reasonable and supportable forecasts of future economic conditions. The Company recorded a recovery of credit loss expense of $1.0 million and $1.0 million as a credit loss expense in the years ended December 31, 2021 and 2020, respectively. The rollforward of the allowance for credit losses is as follows:

| Allowance for credit losses (in thousands): | |
|---|---|
| Beginning balance at January 1, 2020 | $ (1,000) |
| Provision for credit loss expense | — |
| Accounts receivable written-off | — |
| Recoveries | 1,000 |
| Total ending allowance balance as December 31, 2021 | $ — |

**Note 4—Prepaid Expenses and Other**

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

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Current: | | |
| CRO services | $ 340 | $ 1,550 |
| Other clinical development | 2,933 | 2,718 |
| Insurance | 3,178 | 3,708 |
| Professional fees | 398 | 651 |
| Other | 2,135 | 2,635 |
| | 8,984 | 11,262 |
| Long-term: | | |
| CRO services | 166 | 518 |
| Other clinical development | 577 | 437 |
| Other | 611 | 790 |
| | 1,354 | 1,745 |
| Totals | $ 10,338 | $ 13,007 |

Other current prepaid amounts consist primarily of deposits, signing bonuses, licenses, subscriptions and software. Other long-term prepaid amounts consist primarily of deposits, signing bonuses, licenses, subscriptions, software, a capitalized sublease commission and a sublease tenant improvement allowance, net of amortization.

**Note 5—Other Current Assets**

Other current assets consisted of the following at December 31 (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Deposit for manufacturing costs | $ - | $ 3,376 |
| Other | 447 | 265 |
| Totals | $ 447 | $ 3,641 |

Other current asset amounts consist primarily of capitalized sublease commission and a sublease tenant improvement allowances, net of amortization.

**Note 6—Property and Equipment**

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

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Leasehold improvements | $ 3,779 | $ 3,779 |
| Computer equipment | 2,177 | 2,192 |
| Telephone equipment | 302 | 302 |
| Furniture and fixtures | 2,359 | 2,359 |
| | 8,617 | 8,632 |
| Less: accumulated depreciation | (6,861) | (6,151) |
| Totals | $ 1,756 | $ 2,481 |

For the years ended December 31, 2021, 2020, and 2019, the Company incurred depreciation expense of $0.7 million, $0.9 million, and $0.9 million, respectively.

**Note 7—Leases**

In December 2011, the Company entered into a non-cancelable operating lease for office space in Los Angeles, California, which lease was subsequently amended in November 2012, December 2013, March 2014, July 2015, and December 2017. The initial term of the lease was for seven years and commenced on December 10, 2011. As amended, the Company rents approximately 65,656 square feet. The term of the lease runs until March 2026, and rent amounts payable by the Company increase approximately 3% per year. Concurrent with the execution of the lease, the Company provided the landlord an automatically renewable stand-by letter of credit in the amount of $2.0 million. The stand-by letter of credit is collateralized by a high-yield savings account, which is classified as restricted cash, long-term on the accompanying consolidated balance sheets.

In June 2012, the Company entered into a long-term lease agreement for office space in South San Francisco, California, which was subsequently amended in May 2014 and July 2015. As amended, the Company rents approximately 29,470 square feet. The term of this lease runs until March 2026, with the option to extend for an additional five-year term, and rents payable by the Company increase approximately 3% per year. The Company provided the landlord an automatically renewable stand-by letter of credit in the amount of $1.1 million. The stand-by letter of credit is collateralized by a high-yield savings account, which is classified as restricted cash, long-term on the accompanying consolidated balance sheets.

The Company also leases copier equipment for use in the office spaces. Components of copier lease expense include both fixed and variable lease expenses. Total rent expense for each of the respective years ended December 31, 2021 , 2020 and 2019 was approximately $5.1 million. For purposes of determining straight-line rent expense, the lease term is calculated from the date the Company first takes possession of the facility, including any periods of free rent and any renewal option periods that the Company is reasonably certain of exercising. The Company's office and equipment leases generally have contractually specified minimum rent and annual rent increases are included in the measurement of the ROU asset and related lease liability. Additionally, under these lease arrangements, the Company may be required to pay directly, or reimburse the lessors, for real estate taxes, insurance, utilities, maintenance and other operating costs. Such amounts are generally variable and therefore not included in the measurement of the ROU asset and related lease liability but are instead recognized as variable lease expense in selling, general and administrative costs in the consolidated statements of operations when they are incurred.

The future minimum lease payments under ASC 842 as of December 31, 2021 were as follows (in thousands):

| | Amount |
|---|---|
| 2022 | $ 5,483 |
| 2023 | 5,631 |
| 2024 | 5,805 |
| 2025 | 5,983 |
| 2026 | 1,508 |
| **Total minimum lease payments** | $ 24,410 |
| Less: imputed interest | (4,861) |
| **Total lease liabilities** | $ **19,549** |

In February 2019, the Company entered into a long-term sublease agreement for 12,429 square feet of the office space in Los Angeles, California. The term of the lease runs until March 2026, and rent amounts payable to the Company increase approximately 3% per year. The Company recorded operating sublease income of $0.5 million, $0.4 million and $0.2 million for the years ended December 31, 2021, 2020 and 2019, respectively, in other income (expenses) in the consolidated statements of operations.

The future minimum lease payments to be received as of December 31, 2021 were as follows (in thousands):

| | Amount |
|---|---|
| 2022 | $ 481 |
| 2023 | 495 |
| 2024 | 510 |
| 2025 | 525 |
| 2026 | 133 |
| **Total** | $ **2,144** |

Supplemental cash flow information related to leases for the year ended December 31, 2021:

| | |
|---|---|
| Operating cash flows used for operating leases (in thousands) | $ 5,731 |
| Right-of-use assets obtained in exchange for new operating lease liabilities | — |
| Weighted average remaining lease term (in years) | 4.2 |
| Weighted average discount rate | 10.9% |

**Note 8—Intangible Assets**

Intangible assets consisted of the following at December 31 (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Acquired and in-licensed rights | $ 90,000 | $ 90,000 |
| Less: accumulated amortization | (23,875) | (15,860) |
| Total intangible asset, net | $ 66,125 | $ 74,140 |

Estimated future intangible amortization expense as of December 31, 2021 is as follows (in thousands):

| | |
|---|---|
| 2022 | $ 8,015 |
| 2023 | 8,015 |
| 2024 | 8,015 |
| 2025 | 8,015 |
| 2026 | 8,015 |
| Thereafter | 26,050 |
| Totals | $ 66,125 |

**Note 9—Accrued Expenses**

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

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Current: | | |
| Accrued legal verdict expense | $ 57,137 | $ 22,724 |
| Accrued royalties | 8,829 | 8,604 |
| Accrued CRO services | 2,663 | 3,474 |
| Accrued variable consideration | 11,406 | 9,014 |
| Accrued bonus | 5,083 | 7,788 |
| Accrued compensation | 3,878 | 4,820 |
| Accrued other clinical development | 911 | 1,904 |
| Accrued professional fees | 672 | 1,420 |
| Accrued legal fees | 674 | 383 |
| Accrued manufacturing costs | 690 | 752 |
| Other | 632 | 442 |
| | 92,575 | 61,325 |
| Long-term: | | |
| Accrued legal verdict expense | — | 24,822 |
| Accrued CRO services | 878 | 908 |
| Accrued other | 37 | 233 |
| | 915 | 25,963 |
| Totals | $ 93,490 | $ 87,288 |

On October 29, 2021, the parties to the Company's class action lawsuit, *Hsu v. Puma Biotechnology, Inc. et al,* informed the court that they had reached a settlement in principle, and the court entered judgement in the amount of claimed damages and prejudgement interest totaling approximately $54.2 million. On November 2, 2021, the court dismissed the case in light of the parties' settlement, retaining jurisdiction only for settlement approval. The parties' settlement in principle provides that there will be no judgment for liability entered against the Company or its chief executive officer, Alan Auerbach, and provides for payment by the Company of approximately $54.2 million. The first payment of $27.2 million was made in January of 2022 with the balance remaining due in June of 2022.

Also included in accrued legal verdict expense is approximately $2.9 million that may be owed to the plaintiff as a result of the jury verdict in *Eshelman v. Puma Biotechnology, Inc., et al.* The Company estimates the high end of potential damages in the matter could be approximately $2.9 million which also represents the estimate as the most likely outcome; however, the actual amount of damages payable by the Company is still uncertain and will be ascertained only after the completion of the appeal process and subsequent proceedings on remand, and such amount could be greater than the amount of expense already recognized or high end of the estimate. The Company continues to classify the accrual as a current liability due to the uncertainty of timing and amount of the payment.

Accrued variable consideration represents estimates of adjustments to product revenue, net for which reserves are established. Accrued royalties represent royalties incurred in connection with the Company's license agreement with Pfizer. Accrued CRO services, accrued other clinical development expenses, and accrued legal fees represent the Company's estimates of such costs and are recognized as incurred. Accrued compensation includes commissions, vacation and restructuring costs.

Other long-term accrued expenses consists primarily of business license fees, one half of the portion of employer Social Security payroll taxes deferred under the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act") and other taxes, insurance, and marketing fees.

**Restructuring Costs**

On November 2, 2021, the Company implemented a restructuring of the organization in part due to the impact of COVID-19 on the Company's sales. The restructuring included a reduction in headcount of approximately 13%, consisting primarily of the commercial and research personnel. The Company incurred approximately $1.2 million in severance related expense which included salary, health insurance and sales commissions. As of December 31, 2021, approximately $0.1million had not yet been paid. The Company anticipates all restructuring related amounts will be paid by the end of the first quarter of 2022.

**Note 10—Debt**

Long-term debt consisted of the following at December 31, 2021 (in thousands):

| | December 31, 2021 | Maturity Date |
|---|---|---|
| Total debt, inclusive of $2.0 million exit payment | $ 102,000 | July 23, 2026 |
| Less: deferred issuance costs and discounts | (4,908) | |
| Total long-term debt, net | $ 97,092 | |

**Oxford Loan and Security Agreement**

In October 2017, the Company entered into a loan and security agreement with Silicon Valley Bank ("SVB"), as administrative agent, and the lenders party thereto from time to time, or the Original Lenders, including Oxford Finance LLC, ("Oxford"), and SVB. Pursuant to the terms of the credit facility provided for by the loan and security agreement, or the Original Credit Facility, the Company borrowed $50.0 million. In May 2018, the Company entered into an amendment to the loan and security agreement, which provided for an amended credit facility, or the Amended Credit Facility. Under the Amended Credit Facility, the Original Lenders agreed to make term loans available to the Company in an aggregate amount of $155.0 million, consisting of (i) an aggregate amount of $125.0 million, the proceeds of which, in part, were used to repay the $50.0 million outstanding under the Original Credit Facility, and (ii) an aggregate amount of $30.0 million that was drawn in December 2018, which was available under the Amended Credit Facility as a result of achieving a specified minimum revenue milestone.

The term loans under the Amended Credit Facility bore interest at an annual rate equal to the greater of (i) 8.25% 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 preceded the month in which the interest accrued, plus (b) 3.5%. The Company was required to make monthly interest-only payments on each 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 July 1, 2020. Commencing on July 1, 2020, and continuing on the first calendar day of each calendar month thereafter, the Company would have been required to make consecutive equal monthly payments of principal, together with applicable interest, in arrears to each original lender, calculated pursuant to the Amended Credit Facility. All unpaid principal and accrued and unpaid interest with respect to each term loan would have been due and payable in full on May 1, 2023. Upon repayment of the term loans, the Company was also required to make a final payment to the Original Lenders equal to 7.5% of the original principal amount of term loans funded.

On June 28, 2019, or the Effective Date, the Company entered into an amendment and restatement of the loan and security agreement, which provided for a new credit facility, or the New Credit Facility, with Oxford, as collateral agent, and the lenders party thereto from time to time, including Oxford, pursuant to which the Company repaid the $155.0 million outstanding under the Amended Credit Facility, as well as applicable exit and prepayment fees, owed to the Original Lenders under the Amended Credit Facility, using cash on hand and $100.0 million in new borrowings from the New Credit Facility. Under the New Credit Facility, the Company issued to Oxford new and/or replacement secured promissory notes in an aggregate principal amount for all such promissory notes of $100.0 million evidencing the New Credit Facility.

The New Credit Facility was secured by substantially all of the Company's personal property other than intellectual property. The Company also pledged 65% of the issued and outstanding capital stock of its subsidiaries, Puma Biotechnology Ltd. and Puma Biotechnology B.V. The New Credit Facility limited the Company's ability to grant any interest in intellectual property to certain permitted licenses and permitted encumbrances set forth in the agreement.

The term loans under the New Credit Facility bore interest at an annual rate equal to the greater of (i) 9.0% and (ii) the sum of (a) the "primate rate" as reported in The Wall Street Journal on the last business day of the month that immediately preceded the month in which the interest will accrue, plus (b) 3.5%. The Company was required to make monthly interest-only payments on each term loan under the New Credit Facility 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 August 1, 2021, or the Amortization Date. Commencing on the Amortization Date, and continuing on the first calendar day of each calendar month thereafter, the Company was required to make consecutive equal monthly payments of principal, together with applicable interest, in arrears to each lender under the New Credit Facility, calculated pursuant to the New Credit Facility. All unpaid principal and accrued and unpaid interest with respect to each term loan under the New Credit Facility was due and payable in full on June 1, 2024, or the Maturity Date. Upon repayment of such term loans, the Company was also required to make a final payment to the lenders equal to 7.5% of the aggregate principal amount of such term loans outstanding as of the Effective Date. As of December 31, 2020, the effective interest rate for the loan was 12.75%.

The Company had the option to prepay the outstanding principal balance of any term loan in whole but not part, subject to the prepayment fee of 3.0% of any prepaid if the prepayment occurred through and including the first anniversary of the funding date of such term loan, 2.0% of the amount prepaid if the prepayment occurred 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, and 1.0% of the amount prepaid if the prepayment occurred after the second anniversary of the funding date of such term loan and prior to the Maturity Date.

The New Credit Facility included affirmative and negative covenants applicable to the Company, its current subsidiaries and any subsidiaries the Company created in the future. The affirmative covenants included, among others, covenants requiring the Company to maintain its legal existence and governmental approvals, to deliver certain financial reports, to maintain insurance coverage and to satisfy certain requirements regarding deposit accounts. The Company was also required to achieve certain product revenue targets, measured as of the last day of each fiscal quarter on a trailing year to date basis. New minimum revenue levels were to be established for each subsequent fiscal year by mutual agreement of the Company, Oxford, as collateral agent, and the new lenders. The negative covenants included, among others, restrictions on the Company’s transferring of 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.

On February 27, 2020, the Company and Oxford amended the New Credit Facility to establish the Company's minimum revenue thresholds for the trailing year-to-date periods ending March 31, June 30, September 30 and December 31, 2020 and the fiscal year 2021. On August 5, 2020 the Company and Oxford amended the New Credit Facility to amend the minimum revenue thresholds for the trailing year-to-date periods ending September 30 and December 31, 2020. On February 3, 2021, the Company and Oxford amended the New Credit Facility to establish the Company's minimum revenue thresholds for the trailing year-to-date periods ending March 31, June 30, September 30 and December 31, 2021.

The New Credit Facility also included 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 have provided Oxford, as collateral agent, with the right to exercise remedies against the Company and the collateral securing the New Credit Facility, including foreclosure against the property securing the New Credit Facility, including the Company's cash. These events of default included, among other things, the Company's failure to pay principal or interest due under the New Credit Facility, a breach of certain covenants under the New Credit Facility, the Company's 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 the Company in an amount greater than $500,000 individually or in the aggregate that remains unsatisfied, unvacated, or unstayed for a period of 10 days after its entry.

On July 23, 2021, the Company used proceeds from the Athyrium Note Purchase Agreement to repay the amounts outstanding under the New Credit Facility, together with applicable exit and prepayment fees, and terminated the New Credit Facility.

**Athyrium Note Purchase Agreement**

The Company issued senior notes for an aggregate principal amount of $100.0 million pursuant to the note purchase agreement dated July 23, 2021, by and among the Company, its subsidiaries, Athyrium Opportunities IV Co-Invest 1 LP ("Athyrium"), as Administrative Agent, and certain other investor parties (the "Note Purchase Agreement"), with an initial maturity date of July 23, 2026 (the "Athyrium Notes"). The Athyrium Notes were issued for face amount of $100.0 million net of an original issue discount of $1.5 million. The Athyrium Notes also require a 2.0% exit payment to be made on each payment of principal. The borrowings under the Athyrium Notes, together with cash on hand, were used to repay the Company's outstanding indebtedness, including the applicable exit and prepayment fees owed to lenders under its Oxford Credit Facility. The Company can borrow up to an additional $25.0 million under the Note Purchase Agreement. The Athyrium Notes are secured by substantially all the Company's assets. The Company incurred $1.9 million of deferred financing costs with the borrowing.

The Athyrium Notes bear interest at an annual rate equal to the sum of (i) 8.0% and (ii) three-month London Interbank Offering Rate (LIBOR) rate where the three-month LIBOR rate cannot be less than 1.5% or greater than 3.5%. (or a comparable or successor rate that gives due consideration to the then prevailing rate used by commercial banks in the United States which rate is reasonably determined by Athyrium). Interest is payable quarterly on the last business day of March, June, September and December each year. Beginning June 30, 2024, principal payments are required to be made quarterly at 11.11% of the original face amount with the remaining balance paid at maturity. Each principal payment will also include a 2.0% exit payment. As of December 31, 2021, the effective interest rate for the loan is 10.98%.

At the Company's option, the Company may prepay the outstanding principal balance of the notes in whole or in part, subject to a prepayment fee of 2.0% of the amount prepaid if the prepayment occurs on or prior to the second anniversary of the issuance date of such notes, plus the present value of remaining interest that would have accrued through and including the second anniversary date, and 2.0% of the amount prepaid if the prepayment occurs after the second anniversary but on or prior to the third anniversary of the issuance date of such notes. In addition, under the Note Purchase Agreement, the Company will be subject to mandatory prepayments of the net cash proceeds received in connection with a Disposition or Involuntary Disposition (as defined), an Extraordinary Receipt (as defined) or a Debt Issuance (as defined).

The Athyrium Notes include affirmative and negative covenants applicable to the Company. The affirmative covenants include, among others, covenants requiring the Company to maintain its legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, and satisfy certain requirements regarding deposit accounts. The negative covenants include, among others, restrictions on the Company's 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. Additionally, the Company may not make legal payments in connection with the Eshelman or class action legal matters exceeding a certain threshold without first raising sufficient additional capital above the threshold. The Company is also required to achieve certain minimum product revenue targets, measured as of the last day of each fiscal quarter on a

trailing year-to-date basis as well as maintain a minimum cash balance. As of December 31, 2021, the Company was in compliance with such covenants.

As of December 31, 2021, the principal balance outstanding under the Athyrium Notes was $100.0 million, representing all of the Company's long-term debt.

The future minimum principal and exit payments under the Athyrium Notes as of December 31, 2021 were as follows (in thousands):

| | Amount |
|---|---|
| 2022 | $ — |
| 2023 | — |
| 2024 | 33,997 |
| 2025 | 45,329 |
| 2026 | 22,674 |
| **Total** | $ **102,000** |

***Debt Issuance Costs and Discounts***

Debt issuance costs and discounts consist of the following (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Debt issuance costs and discounts (Oxford Credit Facility) | $ - | $ 8,668 |
| Debt issuance costs and discounts (Athyrium Notes) | 5,410 | - |
| Less: accumulated amortization | (502) | (3,666) |
| Included in long-term debt | $ 4,908 | $ 5,002 |

Debt issuance costs and discounts are financing costs related to the Company's outstanding debt. Amortization of debt issuance costs is expensed using the effective interest method and is included in interest expense in the consolidated statements of operations. For the years ended December 31, 2021, 2020 and 2019, the Company recorded approximately $2.6 million, $2.0 million, and $1.5 million, respectively, of interest expense related to the amortization of debt issuance costs, discounts and exit fees in the consolidated statements of operations.

**Note 11—Stockholders' Deficit**

**Common Stock**

The Company issued 0, 18,202, and 87,625 shares of common stock upon exercise of stock options during the years ended December 31, 2021, 2020 and 2019, respectively. The Company issued 1,089,120, 864,881 and 790,642 shares of common stock upon vesting of RSUs during the years ended December 31, 2021, 2020 and 2019, respectively.

**Authorized Shares**

The Company has 100,000,000 shares of stock authorized for issuance, all of which are common stock, par value $0.0001 per share.

**Warrants**

In October 2011, the Company issued an anti-dilutive warrant to Alan Auerbach, the Company's founder and Chief Executive Officer. The warrant was issued to provide Mr. Auerbach with the right to maintain ownership of at least 20% of the Company's common stock in the event that the Company raised capital through the sale of its securities in the future.

In connection with the closing of a public offering in October 2012, the exercise price and number of shares underlying the warrant issued to Mr. Auerbach were established and, accordingly, the final value of the warrant became fixed. Pursuant to the terms of the warrant, Mr. Auerbach was able to exercise the warrant to acquire 2,116,250 shares of the Company's common stock at $16 per share until October 4, 2021. On April 1, 2021, the Company's Board of Directors approved an amendment to the terms of the warrant by extending the term until October 4, 2026. The amendment was approved by the Company's stockholders on June 15, 2021.

As a result of this amendment, the Company recorded additional stock-based compensation in the amount of $13.6 million which was included in the selling, general and administrative expense for the year ended December 31, 2021. The fair value of the additional stock-based compensation was estimated using the Black-Scholes Option Pricing Method (see Note 2-Significant Accounting Policies) with the following assumptions as of June 15, 2021, the date of the modification.

| | |
|---|---|
| Dividend yield | 0.0% |
| Expected volatility | 87.0% |
| Risk-free interest rate | 0.8% |
| Expected life in years | 5.31 |

**Stock Options and Restricted Stock Units**

The Company's 2011 Incentive Award Plan ("2011 Plan") was adopted by the Company's Board of Directors on September 15, 2011. Pursuant to the 2011 Plan, the Company may grant incentive stock options and nonqualified stock options, as well as other forms of equity-based compensation. Incentive stock options may be granted only to employees, while consultants, employees, officers and directors are eligible for the grant of nonqualified options under the 2011 Plan. The maximum term of stock options granted under the 2011 Plan is 10 years and the awards generally vest over a three-year period. The exercise price of incentive stock options granted under the 2011 Plan must be at least equal to the fair value of such shares on the date of grant. On April 1, 2021, the Board of Directors adopted an amendment to the 2011 Plan to increase the number of shares of the Company's common stock reserved for issuance thereunder by 2,000,000 shares. The amendment was approved by the Company's stockholders on June 15, 2021. As of December 31, 2021, a total of 14,545,860 shares of the Company's common stock have been reserved for issuance under the 2011 Plan.

As of December 31, 2021, 5,068,592 shares of the Company's common stock are issuable upon the exercise of outstanding awards granted under the 2011 Plan and 4,159,934 shares of the Company's common stock are available for future issuance under the 2011 Plan. The Company awarded only "plain vanilla options" as determined by the SEC Staff Accounting Bulletin 107, or *Share Based Payment*. The fair value of options granted to employees and non-employees was estimated using the Black-Scholes Option Pricing Method (see Note 2-Significant Accounting Policies) with the following weighted-average assumptions used during the years ended December 31:

| | 2021 | 2020 |
|---|---|---|
| Dividend yield | 0.0% | 0.0% |
| Expected volatility | 86.6% | 100.6% |
| Risk-free interest rate | 0.8% | 0.9% |
| Expected life in years | 5.82 | 5.81 |

The Company's 2017 Employment Inducement Incentive Award Plan ("2017 Plan") was adopted by the Company's Board of Directors on April 27, 2017. Pursuant to the 2017 Plan, the Company may grant stock options and restricted stock units, as well as other forms of equity-based compensation to employees, as an inducement to join the Company. The maximum term of stock options granted under the 2017 Plan is 10 years and the awards generally vest over a three-year period. The exercise price of stock options granted under the 2017 Plan must be at least equal to the fair market value of such shares on the date of grant. On July 15, 2021, the Board of Directors adopted an amendment to the 2017 Plan to increase the number of shares of the Company's common stock reserved for issuance thereunder by 1,000,000 shares. As of December 31, 2021, a total of 3,000,000 shares of the Company's common stock have been reserved for issuance under the 2017 Plan. As of December 31, 2021, 925,972 shares of the Company's common stock are issuable upon the exercise of outstanding stock options and vesting of RSUs granted under the 2017 Plan, and 1,454,340 shares of the Company's common stock are available for future issuance under the 2017 Plan.

Stock-based compensation expense was as follows for the years ended December 31 (in thousands):

| | For the Year Ended December 31, | | |
|---|---|---|---|
| | 2021 | 2020 | 2019 |
| Stock-based compensation: | | | |
| Options - | | | |
| Selling, general, and administrative | $ 3,873 | $ 3,937 | $ 9,044 |
| Research and development | 573 | 3,018 | 7,452 |
| Restricted stock units - | | | |
| Selling, general, and administrative | 8,239 | 13,841 | 18,848 |
| Research and development | 6,361 | 15,779 | 21,983 |
| Warrant Modification - | | | |
| Selling, general, and administrative | 13,587 | - | - |
| Total stock-based compensation expense | $ 32,633 | $ 36,575 | $ 57,327 |

Activity with respect to options granted under the 2011 and 2017 Plan is summarized as follows:

| | Shares | Weighted Average Exercise Price | Weighted Average Remaining Contractual Term (years) | Aggregate Intrinsic Value (in thousands) |
|---|---|---|---|---|
| Outstanding at December 31, 2019 | 5,042,325 | $ 82.42 | 5.2 | $ 1,951 |
| Granted | 700,853 | $ 10.03 | 9.2 | $ - |
| Exercised | (18,202) | $ 3.75 | | $ 119 |
| Expired | (715,634) | $ 90.51 | | $ - |
| Outstanding at December 31, 2020 | 5,009,342 | $ 71.42 | 5.1 | $ 3,458 |
| Granted | 640,748 | $ 11.12 | 8.2 | $ - |
| Forfeited | (186,339) | $ 10.60 | | $ - |
| Expired | (868,504) | $ 87.55 | | $ - |
| Outstanding at December 31, 2021 | 4,595,247 | $ 62.43 | 4.5 | $ - |
| Nonvested at December 31, 2021 | 835,297 | $ 10.64 | 8.9 | $ - |
| Exercisable | 3,759,950 | $ 73.93 | 3.6 | $ - |

At December 31, 2021, total estimated unrecognized compensation cost related to non-vested stock options granted prior to that date was approximately $5.1 million, which is expected to be recognized over a weighted-average period of 1.8 years. At December 31, 2021, the total estimated unrecognized compensation cost related to non-vested RSUs was approximately $11.0 million, which is expected to be recognized over a weighted-average period of 1.6 years. The weighted-average grant date fair value of options granted during the years ended December 31, 2021, 2020 and 2019, was $7.90, $7.81 and $12.08 per share, respectively. The weighted average grant date fair value of RSUs awarded during the year ended December 31, 2021, 2020 and 2019 was $11.44, $10.47 and $14.72, respectively.

**Stock Option Rollforward**

| | Shares | Weighted Average Grant-Date Fair Value |
|---|---|---|
| Nonvested shares at December 31, 2019 | 439,194 | $ 19.38 |
| Granted | 700,853 | $ 7.81 |
| Vested/Issued | (240,375) | $ 25.57 |
| Nonvested shares at December 31, 2020 | 899,672 | $ 8.71 |
| Granted | 640,748 | $ 7.90 |
| Vested/Issued | (518,784) | $ 9.51 |
| Forfeited | (186,339) | $ 7.96 |
| Nonvested shares at December 31, 2021 | 835,297 | $ 7.76 |

**Restricted Stock Unit Rollforward**

| | Shares | Weighted Average Grant-Date Fair Value |
|---|---|---|
| Nonvested shares at December 31, 2019 | 1,991,125 | $ 27.63 |
| Granted | 1,234,616 | $ 10.47 |
| Vested/Issued | (864,881) | $ 36.86 |
| Forfeited | (506,655) | $ 21.72 |
| Nonvested shares at December 31, 2020 | 1,854,205 | $ 13.51 |
| Granted | 1,409,733 | $ 11.44 |
| Vested/Issued | (1,089,120) | $ 14.99 |
| Forfeited | (775,501) | $ 12.13 |
| Nonvested shares at December 31, 2021 | 1,399,317 | $ 11.03 |

**Note 12—401(k) Savings Plan**

During 2012, the Company adopted a 401(k) savings plan for the benefit of its employees. The Company is required to make matching contributions to the 401(k) plan equal to 100% of the first 3% of wages deferred by each participating employee and 50% on the next 2% of wages deferred by each participating employee. The Company incurred expenses for employer matching contributions of approximately $1.5 million, $1.4 million, and $1.5 million for the years ended December 31, 2021, 2020 and 2019, respectively.

**Note 13—Income Taxes**

The Company uses the asset and liability method of accounting for income taxes in accordance with ASC Topic 740, Income Taxes. Under this method, income tax expense is recognized for the amount of: (i) taxes payable or refundable for the current year and (ii) deferred tax consequences of temporary differences resulting from matters that have been recognized in an entity's financial statements or tax returns. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in the results of operations in the period that includes the enactment date. Income tax expense was as follows for the years ended December 31 (in thousands):

| | 2021 | 2020 | 2019 |
|---|---|---|---|
| Current: | | | |
| Federal | $ - | $ - | $ - |
| State | 77 | 124 | 53 |
| Foreign | 247 | 83 | - |
| | 324 | 207 | 53 |
| Deferred: | | | |
| Federal | - | - | - |
| State | - | - | - |
| | - | - | - |
| Total | $ 324 | $ 207 | $ 53 |

The provision for income taxes in the accompanying consolidated statements of operations differs from the amount calculated by applying the statutory income tax rate to loss from continuing operations before income taxes. Approximately $22.5 million of tax expense for the year ended December 31, 2021 is due to stock-based compensation expense shortfall and the expiration of vested stock options. Approximately $3.9 million of the tax benefit for the year-ended December 31, 2021 is due to R&D tax credits, net of an approximately $1.0 million reserve related to unrecognized tax benefits for the method of allocation of expenses used in the R&D tax credits calculation. The primary components of such differences are as follows as of December 31 (in thousands):

| | 2021 | 2020 | 2019 |
|---|---|---|---|
| Tax computed at the federal statutory rate | $ (6,045) | $ (12,540) | $ (15,830) |
| State taxes | (1,072) | (2,304) | (2,453) |
| Foreign taxes | 247 | 83 | — |
| Permanent items | 22,689 | 13,660 | 21,834 |
| R&D credits | (3,941) | (5,231) | (14,946) |
| Prior year adjustment | 916 | (2,116) | (2,792) |
| Change in valuation allowance | (12,470) | 8,655 | 14,240 |
| Total provision | $ 324 | $ 207 | $ 53 |

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

| | 2021 | 2020 | 2019 |
|---|---|---|---|
| Deferred tax assets: | | | |
| Net operating loss carryforwards | $ 258,390 | $ 261,472 | $ 260,555 |
| Business credit carryforwards | 59,514 | 55,574 | 50,343 |
| Compensation | 40,647 | 58,112 | 60,967 |
| Accrued legal verdict | 14,144 | 11,880 | 7,624 |
| Carryforward of disallowed interest | 4,537 | 3,093 | 2,839 |
| Accrued expenses | 104 | 561 | 9 |
| Lease liabilities | 4,839 | 5,657 | 6,145 |
| Other deferred tax assets | 1,306 | 804 | 13 |
| Subtotal | 383,481 | 397,153 | 388,495 |
| Deferred tax liabilities: | | | |
| Lease right-of-use assets | (3,470) | (4,099) | (4,505) |
| Inventory | 406 | (21) | — |
| Other deferred tax liabilities | (318) | (464) | (76) |
| Subtotal | (3,382) | (4,584) | (4,581) |
| Total deferred tax assets | 380,099 | 392,569 | 383,914 |
| Valuation allowance | (380,099) | (392,569) | (383,914) |
| Net deferred tax assets | $ — | $ — | $ — |

As the ultimate realization of the potential benefits of the Company's deferred tax assets is considered unlikely by management, the Company has offset the deferred tax assets attributable to those potential benefits through valuation allowances. Accordingly, the Company did not recognize any benefit from income taxes in the accompanying consolidated statements of operations to offset its pre-tax losses. The valuation allowance decreased by approximately $12.5 million and increased by approximately $8.7 million for the years ended December 31, 2021 and 2020, respectively. At December 31, 2021, the Company had federal and state net operating loss carryforwards, respectively, of approximately $950.2 million and approximately $871.0 million, which will begin to expire in 2033. At December 31, 2021, the Company also has federal research and development credit carryforwards of approximately $39.7 million. If not utilized, the carryforwards will begin to expire in 2033. The Company has state research and development credit carryforwards of approximately $24.1 million which do not expire. Pursuant to the Internal Revenue Code, Sections 382 and 383, use of the Company's net operating loss and credit carryforwards could be limited if a cumulative change in ownership of more than 50% occurs within a three-year period. The Company performed an initial assessment of the potential limitation on net operating loss and credit carryforwards, and concluded that there will be no limitation for the tax year 2021.

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

| | 2021 | 2020 | 2019 |
|---|---|---|---|
| Unrecognized tax benefits - January 1 | $ 3,276 | $ 1,968 | $ 8,777 |
| Gross decreases - tax positions in a prior period | — | — | (8,422) |
| Gross increases - tax positions in a current period | 985 | 1,308 | 1,613 |
| Unrecognized tax benefits - December 31 | $ 4,261 | $ 3,276 | $ 1,968 |

During the year ended December 31, 2019, the Company completed an R&D credit study. As a result of the study, the Company assessed that the Company qualified under safe harbor rules, which when applied consistently results in a more conservative approach of calculating the amount of R&D credit. The Company concluded that a release of uncertain tax benefits was appropriate and released a portion of previously recorded uncertain tax positions reserve. There were no releases of uncertain tax position reserves in the year ended December 31, 2021. Current year increases in the R&D credit relate to R&D support department costs that were allocated to various research projects based upon a reasonable methodology. The uncertain tax position is related to the method of allocating these costs.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by the federal and state jurisdictions where applicable. There are currently no pending income tax examinations. The Company's tax years for 2009 and forward are subject to examination by the federal and California tax authorities due to the carryforward of unutilized net operating losses and research and development credits.

**Note 14—Commitments and Contingencies**

**License Agreement**

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

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

As consideration for the license, the Company is required to make substantial payments upon the achievement of certain milestones totaling approximately $187.5 million if all such milestones are achieved, of which $90.0 million have been achieved as of December 31, 2021. In connection with the FDA approval of NERLYNX in July of 2017, the Company triggered a one-time milestone payment pursuant to the agreement. In June 2020, the Company entered into a letter agreement, or the Letter Agreement, with Pfizer relating to the method of payment associated with a one-time milestone payment under the license agreement with Pfizer. The Letter Agreement permitted the Company to make the milestone payment in installments with the remaining amount payable to Pfizer (including interest). The milestone payment accrued interest at 6.25% per annum. The milestone payment including accrued interest of $1.8 million was paid in full in September 2021. The installment payments and accrued interest are included in accrued in-licensed rights on the accompanying consolidated balance sheets. The Company may trigger additional milestone payments in the future. Should the Company commercialize any more of the compounds licensed from Pfizer or any products containing any of these

compounds, the Company will be obligated to pay to Pfizer annual royalties at a fixed rate in the low to mid-teens of net sales of all such products, subject to certain reductions and offsets in some circumstances. The Company's royalty obligation continues, on a product-by-product and country-by-country basis, until the later of (i) the last to expire 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 in such country or expiration of a certain time period after first commercial sale of such licensed product in such country. In the event that the Company sublicenses the rights granted to the Company under the license agreement with Pfizer to a third party, the same milestone and royalty payments are required. The Company can terminate the license agreement at will, or for safety concerns, in each case upon specified advance notice.

**Clinical Trial Contracts**

The Company engages with CROs and contract manufacturing organizations ("CMOs") in addition to engaging in contracts for the management of its ongoing clinical trials and pre-commercialization efforts. The Company may cancel these agreements with a 30 to 45 day written notice to the outside vendor. The Company would be obligated to pay for services rendered up to that point, which amounts to total contractual obligations of approximately $54.8 million within the next twelve months. The contracts also contain variable costs that are hard to predict as they are based on such things as patients enrolled and clinical trial sites, which can vary, and therefore, are not included in the total obligations amount. Included in the total contractual obligations amount above are payments to be made when milestones are reached. As of December 31, 2021, Company obligations for potential milestone payments totaled approximately $17.3 million. This amount will be paid by the Company if all milestones are reached and would reduce the overall contractual obligation if one or more milestone is never reached.

**Legal Proceedings**

The Company and certain of its executive officers were named as defendants in the lawsuits detailed below. The Company records a liability in the consolidated financial statements for loss contingencies when a loss is known or considered probable and the amount can be reasonably estimated. If the reasonable estimate of a known or probable loss is a range, and no amount within the range is a better estimate than any other, the minimum amount of the range is accrued. If a loss is reasonably possible but not known or probable, and can be reasonably estimated, the estimated loss or range of loss is disclosed. When determining the estimated loss or range of loss, significant judgment is required to estimate the amount and timing of a loss to be recorded. Currently, the Company has accrued estimated losses of $54.2 million related to *Hsu v. Puma Biotechnology, Inc., et al.,* and $2.9 million related to *Eshelman v. Puma Biotechnology, Inc., et al.* as detailed below. For certain legal expenses related to the verdicts listed below, the Company has received reimbursements from its insurers.

***Hsu v. Puma Biotechnology, Inc., et al.***

On June 3, 2015, Hsingching Hsu, individually and on behalf of all others similarly situated, filed a class action lawsuit against the Company and certain of its executive officers in the United States District Court for the Central District of California (Case No. 8:15-cv-00865-AG-JCG). On October 16, 2015, lead plaintiff Norfolk Pension Fund filed a consolidated complaint on behalf of all persons who purchased the Company's securities between July 22, 2014 and May 29, 2015. A trial on the claims relating to four statements alleged to have been false or misleading was held from January 15, 2019 to January 29, 2019. At trial, the jury found that three of the four challenged statements were not false or misleading, and thus found in the defendants' favor on those claims. The jury found liability as to one statement and awarded a maximum of $4.50 per share in damages, which represents approximately 5% of the total claimed damages of $87.20 per share. On September 9, 2019, the Court entered an order specifying the rate of prejudgment interest to be awarded on any valid claims at the 52-week Treasury Bill rate. On September 8, 2020, the claims administrator submitted its final claims report to the Court and, on October 9, 2020, the claims administrator submitted its supplemental claims report. The claims report reflects approximately $50.5 million in claimed damages. The Company initially disagreed with the amount of claimed damages. On November 27, 2020, the Court issued an order setting out the process for challenging claims.

On October 29, 2021, the parties informed the court that they had reach a settlement in principle, and the court entered judgment in the amount of claimed damages and prejudgment interest totaling approximately $54.2 million. On November 2, 2021, the court dismissed the case in light of the parties' settlement, retaining jurisdiction only for settlement approval. The parties' settlement in principle provides that there will be no judgment for liability entered against the Company or its chief executive officer, Alan Auerbach, and provides for payment by the Company of approximately $54.2 million in two installments, to be paid in January and June of 2022. The settlement in principle is subject to execution of a formal settlement agreement to be negotiated among the parties, which agreement will be submitted to the court for approval.

It is reasonably possible that the final total damages awarded will differ from these estimates; however, the amount is not estimable at this time. A final judgment has not yet been entered; however, the Company made the first installment payment in January 2022, see Note 15-Subsequent Events.

***Eshelman v. Puma Biotechnology, Inc., et al.***

In February 2016, Fredric N. Eshelman filed a lawsuit against the Company's Chief Executive Officer and President, Alan H. Auerbach, and the Company in the United States District Court for the Eastern District of North Carolina (Case No. 7:16-cv-00018-D). The complaint generally alleged that Mr. Auerbach and the Company made defamatory statements regarding Dr. Eshelman in connection with a proxy contest. In May 2016, Dr. Eshelman filed a notice of voluntary dismissal of the claims against Mr. Auerbach. A trial on the remaining defamation claims against the Company took place from March 11 to March 15, 2019. At trial, the jury found the Company liable and awarded Dr. Eshelman $15.9 million in compensatory damages and $6.5 million in punitive damages. The Company strongly disagreed with the verdict and, on April 22, 2019, filed a motion for a new trial or, in the alternative, a reduced damages award. The Court denied that motion on March 2, 2020. The Company has appealed that ruling, and the verdict. Additionally, after trial, the plaintiff filed a motion seeking approximately $3.0 million in attorneys' fees, as well as prejudgment interest. In the Court's March 2020 ruling, it denied the motion for attorneys' fees but granted the request for prejudgment interest, bringing the total judgment to $26.3 million. On March 30, 2020, the plaintiff filed a notice of cross-appeal and conditional cross-appeal, appealing the Court's order denying the plaintiff's request for attorneys' fees and conditionally cross-appealing a Court ruling that certain communications between Mr. Auerbach and his attorneys were protected by attorney-client privilege and a related evidentiary ruling. On June 23, 2021, the United States Court of Appeals for the Fourth Circuit affirmed the liability verdict in the *Eshelman v. Puma Biotechnology, et al* matter but found the $22.4 million damages award, payable by the Company, to be excessive in light of the evidence at trial. The court vacated this award and remanded for a new trial on damages. The Court's judgment will eliminate the damages award, including interest on the judgment, pending further proceedings on remand. On July 7, 2021, the plaintiff filed a petition for panel or en banc rehearing, which was denied on July 20, 2021. On July 26, 2021, the plaintiff filed a motion to stay issuance of the Fourth Circuit's mandate pending the filing and resolution of a petition for certiorari in the Supreme Court. The Fourth Circuit denied that motion on July 29, 2021. On October 18, 2021, the plaintiff filed a petition of certiorari with the Supreme Court seeking review of the Fourth Circuit's ruling, which was denied on December 13, 2021. We estimate the high end of potential damages in the matter could be approximately $2.9 million which also represents our estimate as the most likely outcome.

Due to the appeal, the Company secured a bond for the potential damages, which is collateralized by an automatically renewable stand-by letter of credit in the amount of $8.9 million. The stand-by letter of credit is collateralized by a high-yield savings account, which is classified as restricted cash, current on the accompanying consolidated balance sheets.

***CANbridge Licensing Dispute***

On July 28, 2020, the Company filed a request for arbitration against CANbridge Biomed Limited ("CANbridge") before the ICC International Court of Arbitration. The Company asserted that CANbridge violated the terms of the Company's agreement with CANbridge in which it granted CANbridge an exclusive sublicense to develop and commercialize NERLYNX throughout greater China. The Company sought an arbitral award, as well as damages, costs, and attorneys' fees. On August 26, 2020, CANbridge filed its response to the Company's request for arbitration and brought counterclaims, seeking damages, costs and attorneys' fees. On February 24, 2021, the parties resolved their dispute, with each side agreeing to dismiss their respective claims in the arbitration. The settlement is limited to claims asserted in the arbitration, or that are related to the claims asserted in the arbitration.

***Legal Malpractice Suits***

On September 17, 2020, the Company filed a lawsuit against Hedrick Gardner Kincheloe & Garofalo, L.L.P. and David L. Levy, the attorneys who previously represented the Company in *Eshelman v. Puma Biotechnology, Inc., et al.* in the Superior Court of Mecklenburg County, North Carolina. The Company is alleging legal malpractice based on the defendants' negligent handling of the defense of the Company in *Eshelman v. Puma Biotechnology, Inc., et al*. as detailed above. The Company is seeking recovery of the entire amount awarded in *Eshelman v. Puma Biotechnology, Inc., et al.* On November 23, 2020, the defendant filed an answer to the complaint denying the allegations of negligence.

On June 23, 2021, the United States Court of Appeals for the Fourth Circuit set aside the damages award in the *Eshelman v. Puma Biotechnology, Inc., et al* matter and remanded the case to the District Court for a new trial on damages. On October 7, 2021, Judge R. Stuart Albright entered into an Order staying all proceedings in the legal malpractice case for six months to allow time to resolve the damages issues in the Eshelman case. As a result, the amount of any potential damages that may be recovered in the legal malpractice case is uncertain at this time.

***Patent-Related Proceedings***

*AstraZeneca Litigation*

On September 22, 2021, the Company filed suit against AstraZeneca Pharmaceuticals, LP, AstaZeneca AB, and AstraZeneca PLC for infringement of United States Patent Nos. 10,603,314 ("the '314 patent") and 10,596,162 ("the '162 patent"). (*Puma Biotechnology, Inc. et al. v. AstraZeneca Pharmaceuticals LP et al*, 1:21CV01338 (D. Del. Sep. 22, 2021)). The Company's complaint alleges that AstraZeneca's commercial manufacture, use, offer for sale, sale, distribution, and/or importation of Tagrisso® (osimertinib) products for the treatment of gefitinib and/or erlotinib-resistant non-small cell lung cancer infringes the '314 and '162 patents. The Company is an exclusive licensee of the '314 and '162 patents under the Pfizer Agreement. Wyeth is a co-plaintiff. Plaintiffs seek a judgment that AstraZeneca's product infringes the asserted patents and an award of monetary damages in an amount to be proven at trial. AstraZeneca AB and AstraZeneca Pharmaceuticals LP filed an answer and counterclaims on November 5, 2021, including claims challenging the asserted patents are not infringed and/or invalid, and accusing plaintiffs of patent misuse. The parties stipulated to dismiss AstraZeneca PLC as a defendant and Pfizer as a Counterclaim Defendant on December 10, 2021, which the Court so ordered on December 13, 2021. The Company filed its answer to AstraZeneca's counterclaims on December 17, 2021. The case was recently reassigned to visiting Judge Matthew Kennelly of the Northern District of Illinois. The parties filed a joint status report about the case and attended a teleconference with the Court on February 9, 2022. The parties submitted a joint discovery plan and proposed schedule for onsideration by the Court on February 15, 2022. On February 17, 2022, Judge Kennelly entered a schedule for the case, including setting the matter for trial to begin May 13, 2024. The parties will now proceed to fact discovery.

*Sandoz Litigation*

On November 10, 2021, the Company filed suit against Sandoz, Inc. for infringement of U.S. Patent No. 7,399,865 B2 ("the '865 patent") (*Puma Biotechnology, Inc. et al. v. Sandoz Inc.*, 1:21CV19918 (D.N.J. Nov. 10, 2021)**)**. The Complaint was filed within 45 days of Sandoz providing notice of its abbreviated new drug application ("ANDA") seeking approval to market a generic version of Puma's NERLYNX (neratinib) Tablets, 40 mg prior to the expiration of the '865 patent. Puma and Wyeth seek judgment that Sandoz's purported ANDA product would, if allowed on the market, infringe the '865 patent, and ask that the Court order that, pursuant to 35 U.S.C. 271(e)(4)(A), the FDA's approval of the Sandoz ANDA can be no earlier than the date the '865 patent expires. Sandoz has stated that, due to Paragraph III certifications filed for other patents listed in the Orange Book in connection with NERLYNX, Sandoz cannot launch its ANDA product until November 21, 2030 at the earliest. The Company's complaint alleges that Sandoz has infringed the '865 patent by seeking approval to commercially manufacture, use, offer for sale, sell, and/or import a generic version of NERLYNX in the United States prior to the expiration of the '865 patent. Puma is the exclusive licensee of the '865 patent under the Pfizer Agreement. Wyeth is a co-plaintiff. Sandoz submitted its answer to the complaint on January 14, 2022 and asserted counterclaims challenging the '865 patent as invalid. Puma and Wyeth filed an answer to those counterclaims on February 4, 2022. The parties appeared before the Magistrate Judge on February 15, 2022 for an initial hearing, and submitted a scheduling order on February 18, 2022. The filing of Puma's Complaint against Sandoz triggered a 30-month stay of marketing approval for Sandoz's ANDA.

*China Litigation*

On January 18, 2022, a competitor filed an ANDA with the National Medical Products Administration in China ("NMPA") seeking approval to market a generic version of the Company's drug NERLYNX in China. This competitor seeks approval prior to the expiration of three patents listed on the China Patent Information Registration Platform for Marketed Drugs ("Chinese Orange Book"), alleging in a Type 4.2 patent declaration that its generic version of NERLYNX does not fall within the scope of the claims of NERLYNX patents listed on the Chinese Orange Book. The patent declarations of this competitor were published on the Chinese Orange Book on January 19, 2022. The Company and/or its commercialization partner in China have 45 days from the publication of the patent declaration to request administrative or judicial determination that this competitor's generic tablet falls within the scope of the claims of NERLYNX Patents listed on the Chinese Orange Book. Upon acceptance of the request for administrative or judicial determination, NMPA will institute a stay of this competitor's ANDA for nine months. If, during the nine-month stay period, an administrative or judicial determination is made that the generic tablet falls within the scope of the claims of the NERLYNX patents listed on the Chinese Orange Book, NMPA will be prohibited from approving the competitor's ANDA until the NERLYNX patents expire.

**Note 15—Subsequent Events**

In January 2022, the Company paid the first of two equal installment payments which will total approximately $54.2 million per the terms of the Class Action settlement. See Note 14-Commitments and Contingencies for further details.

**Exhibit 31.1**

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

I, Alan H. Auerbach, certify that:

1. I have reviewed this Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021;

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

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

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

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

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

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

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

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

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

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

Date: March 3, 2022

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

**Exhibit 31.2**

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

I, Maximo F. Nougues, certify that:

1. I have reviewed this Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021;

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

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

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

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

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

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

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

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

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

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

Date: March 3, 2022

/s/ Maximo F. Nougues
Maximo F. Nougues
Principal Financial and Accounting Officer

**Exhibit 32.1**

**CERTIFICATION**

**PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO**

**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

The following certification is being furnished solely to accompany the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021, pursuant to 18 U.S.C. § 1350 and in accordance with SEC Release No. 33-8238. This certification shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be incorporated by reference in any filing of Puma Biotechnology, Inc. under the Securities Act of 1933, as amended, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

**Certification of Principal Executive Officer**

I, Alan H. Auerbach, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021, fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended, and that the information contained in such report fairly presents, in all material respects, the financial condition and results of operations of Puma Biotechnology, Inc.

Date: March 3, 2022

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

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

**Exhibit 32.2**

**CERTIFICATION**

**PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO**

**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

The following certification is being furnished solely to accompany the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021, pursuant to 18 U.S.C. § 1350 and in accordance with SEC Release No. 33-8238. This certification shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be incorporated by reference in any filing of Puma Biotechnology, Inc. under the Securities Act of 1933, as amended, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

**Certification of Principal Financial Officer**

I, Maximo F. Nougues, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that the Annual Report on Form 10-K of Puma Biotechnology, Inc. for the year ended December 31, 2021, fully complies with the requirements of Section 13(a) or 15(d), as applicable, of the Securities Exchange Act of 1934, as amended, and that the information contained in such report fairly presents, in all material respects, the financial condition and results of operations of Puma Biotechnology, Inc.

Date: March 3, 2022

/s/ Maximo F. Nougues
Maximo F. Nougues
Principal Financial and Accounting Officer

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

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## COMPANY LEADERSHIP

### BOARD OF DIRECTORS

**Alan H. Auerbach**
Chairman, Chief Executive Officer and President
Puma Biotechnology, Inc.

**Allison Dorval**
Chief Financial Officer
Verve Therapeutics, Inc.

**Michael P. Miller**
Executive Vice President U.S. Commercial (retired)
Jazz Pharmaceuticals plc

**Jay M. Moyes**
Chief Financial Officer
Sera Prognostics, Inc.

**Adrian M. Senderowicz, M.D.**
Senior Advisor
Constellation Pharmaceuticals

**Brian Stuglik, R.Ph.**
Chief Executive Officer
Verastem, Inc.

**Troy E. Wilson, Ph.D., J.D.**
President, Chief Executive Officer and Chairman
Kura Oncology, Inc.

### CORPORATE OFFICERS

**Alan H. Auerbach**
Chairman, Chief Executive Officer and President

**Maximo F. Nougues**
Chief Financial Officer

**Jeff J. Ludwig**
Chief Commercial Officer

**Alvin Wong, Pharm.D.**
Chief Scientific Officer

**Douglas Hunt, B.Sc (Hons).**
Senior Vice President, Regulatory Affairs,
Medical Writing and Project Management

## STOCKHOLDER INFORMATION

**Corporate Headquarters**
Puma Biotechnology, Inc.
10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024
424-248-6500

**Investor Relations**
Securities analysts, investment professionals and stockholders should direct inquiries to Investor Relations at 424-248-6500 Ext. 2011 or ir@pumabiotechnology.com.

For additional information about Puma, please visit our website at https://www.pumabiotechnology.com.

**Common Stock**
Puma's common stock is listed on The Nasdaq Stock Market under the trading symbol "PBYI."

**Transfer Agent**
EQ Shareowner Services℠

Mail:
P.O. Box 64854
St. Paul, MN 55164

Courier:
1110 Centre Pointe Curve, Suite 101
Mendota Heights, MN 55120--4100

Telephone:
800-468-9716
651-450-4064

Website: https://www.shareowneronline.com

**Annual Meeting**
The 2022 Annual Meeting of Stockholders will be held at 1:00 p.m. PDT on Tuesday, June 14, 2022 at
Puma Biotechnology, Inc.
10880 Wilshire Boulevard, Suite 2150
Los Angeles, CA 90024

**Independent Registered Public Accounting Firm**
KPMG LLP
550 South Hope St.
Suite 1500
Los Angeles, CA 90071

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**Forward-Looking Statements**

This document contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, including, but not limited to, statements regarding the commercialization of NERLYNX, the potential indications of the Company's drug candidates and the development of those drug candidates, and the announcement of data relative to the Company's clinical trials. These statements are often, but not always, made through the use of words or phrases such as "anticipates," "estimates," "expects," "may," "will," "would," "plans," "projects," "continuing," "ongoing," "believes," "intends," and similar words or phrases intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Discussions containing these forward-looking statements may be found throughout this document, including the sections entitled "Item 1. Business" and "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021. All forward-looking statements included in this document involve risks and uncertainties that could cause the Company's actual results to differ materially from the anticipated results and expectations expressed in these forward-looking statements. These forward-looking statements are based on current expectations, forecasts and assumptions, and actual outcomes and results could differ materially from those in the forward-looking statements due to a number of factors, which include, but are not limited to, any adverse impact on the Company's business, strategy, plans and objectives of management, future operations and/or financial position, growth opportunities in the market in which the Company operates, or the global economy and financial markets, generally, from the global COVID-19 pandemic, and the risk factors disclosed in the periodic and current reports filed by the Company with the Securities and Exchange Commission from time to time, including the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021, which is included herein. Readers are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made hereof. The Company assumes no obligation to update these forward-looking statements, except as required by law.

**Puma Biotechnology, Inc.**
10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024
pumabiotechnology.com

*"Five years ago, I took a stand against recurrence and that included therapy with NERLYNX .... I'm continually surprised at how many HER2+ patients are still unaware of NERLYNX as a treatment option."*

**VALERIE, a former NERLYNX patient**