Risk Factors Comparison 2025-02-27 to 2024-02-29 Form: 10-K

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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: • While we have reported net income in the years ended December 31 **, 2024** , 2023 and 2022, we cannot assure that we will continue to do so and may not be able to maintain profitability. • We are currently a single product company with limited commercial sales experience. • We may not be able to successfully commercialize NERLYNX in the future. • 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 in- licensed alisertib, a drug candidate for which we have assumed all responsibility for global development and commercialization. Our development of alisertib will be expensive, lengthy and unpredictable, and any failure to successfully develop alisertib will have a material adverse effect on our business and financial position. • 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, alisertib or 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. • We are in the early stages of development of alisertib, and we cannot be certain that we will be successful if we seek regulatory approvals for our drug 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 in the commercialization of NERLYNX, our business, results of operations and financial condition may be materially adversely affected. • We are exposed to the risks associated with reliance on a direct sales force to commercialize NERLYNX in the United States. • Our NERLYNX commercialization efforts may fail to achieve the degree of market acceptance by patients and physicians necessary for commercial success. • 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 certain patients with early stage, HER2- positive breast cancer and the FDA has granted approval for NERLYNX for the treatment of certain patients with metastatic HER2- positive breast cancer, the terms of the approvals may limit its commercial potential. • 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, alisertib and our other 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 public health emergencies or outbreaks of epidemics, pandemics or contagious diseases. • We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm us. • We depend significantly on in- licensed intellectual property, and the termination of these licenses 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. and our wholly owned ~~subsidiaries~~ **subsidiary** . We are a biopharmaceutical company that develops and commercializes innovative products to enhance cancer care and improve treatment outcomes for patients. We are currently commercializing NERLYNX, an oral version of neratinib, for the treatment of HER2- positive breast cancer. Additionally, we have in- licensed, and are responsible for global development and commercialization of, alisertib. Alisertib is a selective, small- molecule inhibitor of ~~aurora~~ **Aurora** ~~kinase~~ **Kinase** A that is designed to disrupt mitosis leading to apoptosis of rapidly proliferating tumor cells that are dependent on ~~aurora~~ **Aurora** ~~kinase~~ **Kinase** A. Prior to our licensing alisertib from Takeda, alisertib was tested in over 1, 300 patients who were treated across 22 company- sponsored trials resulting in a large, well- characterized clinical safety database. Based on information in this database, we believe alisertib has potential application in the treatment of range of different cancer types, including hormone receptor positive breast cancer, triple negative breast cancer, small cell lung cancer and head and neck cancer. We intend to pursue development of alisertib initially in small cell lung cancer and hormone receptor positive breast cancer. The following figure provides an overview of our commercial product and drug candidates. * EBC: Early breast cancer * * MBC: Metastatic breast cancer * * * HRc : Hormone receptor positive * * * * NSCLC: Non **-** small cell lung cancer Neratinib Breast cancer is the leading cause of cancer death among women worldwide, with approximately one 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, 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 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** 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. Neratinib is a potent irreversible **tyrosine kinase inhibitor (“** 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 breast cancer patients who have been previously treated with these existing treatments, most notably due to its irreversible inhibition of the HER2 target enzyme. NERLYNX, the commercial name for neratinib, is currently approved in the United States for two indications: the extended adjuvant treatment of adult patients with early stage HER2- overexpressed / amplified breast cancer following adjuvant trastuzumab- based therapy and for 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 also believe neratinib has potential 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. We currently market NERLYNX in the United States using our direct specialty sales force consisting of approximately ~~38~~ **35** sales specialists as of December 31, ~~2023~~ **2024** . 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. Outside the United States, we have entered into exclusive sub- license agreements with third parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved. As of December 31, ~~2023~~ **2024** , NERLYNX has received approval for the treatment of certain patients with extended adjuvant **and /** or metastatic HER2- positive breast cancer in more than ~~20~~ **40** countries outside the United States, including the European Union (“ EU ”), China, Latin America, Australia, Canada, and Hong Kong. We are currently a 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 NERLYNX. 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 NERLYNX enables participation from countries outside the United States where permitted by applicable rules, procedures and regulatory authorities. The program provides access to NERLYNX 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~~ **the Middle East** ~~must be unable to participate in any ongoing NERLYNX clinical trial~~ . In September 2022, we entered into an exclusive license agreement with a subsidiary of Takeda Pharmaceutical Company Limited (“ Takeda ”) to license the worldwide research and development and commercial rights to alisertib. Alisertib is an investigational, reversible, ATP- competitive inhibitor that is designed to be highly selective for Aurora Kinase A. Inhibition of Aurora Kinase A leads to disruption of mitotic spindle apparatus assembly, disruption of chromosome segregation, and inhibition of cell proliferation. In clinical trials to date, alisertib had shown single agent activity and activity in combination with other cancer drugs in the treatment of many different types of cancers, including hormone receptor positive breast cancer, triple negative breast cancer, small cell lung cancer and head and neck cancer. Alisertib has also shown activity in previous clinical trials in peripheral T cell lymphoma and non- Hodgkin' s lymphoma. Prior to our licensing alisertib from Takeda, the drug was tested in over 1, 300 patients who were treated across 22 company- sponsored trials resulting in a large well- characterized clinical safety database. 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. • Advance the development of alisertib. We intend to pursue the development of alisertib in hormone receptor positive breast cancer **,** as well as small cell lung cancer based on the prior clinical data that has been generated. We also plan to evaluate alisertib in biomarker focused populations where it has shown a higher degree of activity, such as patients with c- ~~myc~~ **Myc** amplification and RB1 loss / RB1 mutations, as we believe that this may provide a point of differentiation from the other drugs being developed in the treatment of these diseases ~~. In the first half of 2024, we plan to initiate our ALI- 4201 clinical trial, a Phase II clinical trial in up to 60 patients designed to evaluate the safety and efficacy of alisertib in extensive small cell lung cancer~~ . • Maximize the value of our programs by maintaining the flexibility to commercialize our drug candidates independently or through collaborative relationships with third parties. We are currently commercializing NERLYNX using a direct sales force in the United States and using sub- licensees in certain countries outside 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 commercial drugs and / or 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 portfolio including commercial drugs where we can successfully leverage our existing commercial infrastructure and a 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. HER2- Positive 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 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 are the combination of trastuzumab and chemotherapy, the combination of pertuzumab plus trastuzumab and chemotherapy, or ~~Kadcyla~~ **KADCYLA ®** , which is approved specifically in patients with HER2- positive early stage breast cancer with residual disease after neoadjuvant treatment. In addition, we are aware of numerous additional ongoing clinical trials involving other drug candidates used alone or in combination with existing drugs to treat patients with breast cancer. 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~~ **KADCYLA** plus tucatinib versus ~~Kadcyla~~ **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~~ **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. Background on 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. Neratinib — Early Stage Breast Cancer Extended Adjuvant Breast Cancer In 2017, the FDA approved NERLYNX (neratinib) 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 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~~ **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 (“ 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 included in the body of the National Comprehensive Cancer Network (“ NCCN ”) Practice Guidelines for Breast Cancer for the treatment of adjuvant HER2- positive Breast Cancer (BINV- 16 & 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. Dose escalation of neratinib is included as an approach to improve the tolerability of neratinib in the treatment of adjuvant HER2- positive breast cancer. 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 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 Colestipol Neratinib Dose Neratinib Dose Loperamide Escalation Escalation Loperamide Budesonide Colestipol Loperamide PRN Scheme 1 Scheme 2 (N = 137) (N = 64) (N = 136) (N = 104) (N = 60) (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 **in** 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. Dose escalation as an approach to improve the tolerability of neratinib in the treatment of adjuvant HER2- positive Breast Cancer (BINV- L) is included in the NCCN treatment guidelines. This inclusion aligns with the labeling supplement to the U. S. Prescribing Information approved by the FDA in June 2021, which incorporated the use of NERLYNX dose escalation as evaluated in the Phase II CONTROL study. Neratinib — Metastatic Breast Cancer In February 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 progression free survival (“ 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 neratinib 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 neratinib for the indication to be studied to support ~~a~~ **an** 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~~ **a** 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 (“ 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. NERLYNX plus capecitabine is included in the body of the NCCN Practice Guidelines for Breast Cancer for the treatment of recurrent unresectable (local or regional) or stage IV (M1) HER2- positive Breast Cancer (BINV- Q), with a recommendation for Fourth Line and Beyond (optimal sequence is not known). Dose escalation of neratinib is included as an approach to improve the tolerability of neratinib in the treatment of metastatic HER2- positive breast cancer. 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 **was evaluated** ~~is currently being tested~~ in a clinical trial ~~in collaboration~~ with **the** Translational Breast Cancer Research Consortium **,** referred to as TBCRC 022. The purpose of ~~this~~ **the** study ~~is~~ **was** to determine how well neratinib ~~works~~ **worked** in treating breast cancer that ~~has~~ **had** spread to the brain. In this research study, the investigators **looked** ~~are looking~~ to see how well neratinib ~~works~~ **worked** to decrease the size of or stabilize breast cancer that ~~has~~ **had** 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~~ **had** brain metastases. The trial **initially** 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 (" 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. Updated results from **an additional** TBCRC ~~–~~022 **cohort** were presented in December 2022 at the 2022 San Antonio Breast Cancer Symposium **.** This presentation outlined updates from three **sub-** cohorts **of cohort 4** : 4A – patients with previously untreated Breast Cancer Brain Metastases (" BCBM "); 4B – patients with BCBM progressing after prior local CNS- directed therapy without prior T- DM1 exposure; and 4C – patients with BCBM progressing after prior local CNS- directed therapy with previous T- DM1 exposure. Patients with measurable HER2- positive BCBM received neratinib 160 mg orally once daily plus T- DM1 3. 6 mg / kg intravenously every 21 days in the three parallel- enrolling cohorts. Diarrhea prophylaxis with colestipol and loperamide was required during cycle 1. All enrolled patients underwent a brain MRI plus CT scan of the chest / abdomen / pelvis every six weeks for 18 weeks, followed by every nine weeks thereafter. The primary endpoint, Response Assessment in Neuro- Oncology- Brain Metastases (" RANO- BM "), was evaluated in each cohort separately. The efficacy results from the trial showed that CNS Objective Response Rate by RANO- BM was 33. 3 % of patients in cohort 4A, 29. 4 % in cohort 4B, and 28. 6 % in cohort 4C. Rates of response stable disease greater than or equal to ~~6~~ **six** months were 50 % in cohort 4A, 35. 3 % in cohort 4B, and 33. 3 % in cohort 4C. Intracranial activity was observed for the combination of neratinib plus T- DM1 in all three cohorts, including in

patients with prior T- DM1 exposure, suggesting a reversal of resistance to T- DM1. Overall, the most frequently observed adverse event was diarrhea, grade 2 (32 %) and grade 3 (23 %). 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 **breast cancer and** brain metastases. The NCCN designated NERLYNX in combination with capecitabine as a category ~~2B~~ **2A** treatment option and NERLYNX in combination with paclitaxel as a category 2B treatment option. Use **of NERLYNX** ~~, 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. Neratinib — Other Potential Applications While we believe neratinib has potential applications in other diseases, such as HER2 ~~Mutation - Positive Solid Tumors, HER2- Mutated~~ **mutated solid tumors** , **as well as** ~~Non- Amplified Breast Cancer and~~ EGFR ~~Exon~~ **exon** 18 ~~- Mutated~~ **mutated** ~~Non~~ **non-** ~~Small~~ **small** ~~Cell~~ **cell** ~~Lung~~ **lung** ~~Cancer~~ **cancer** , we are not currently pursuing additional development in these indications at this time. NERLYNX combinations are included in the body of the NCCN Practice Guidelines for Breast Cancer for patients with HER2- negative metastatic (stage IV) breast cancer and activating mutations in the HER2 gene as detected by next generation sequencing of tumor tissue or ctDNA under the heading Useful in Certain Circumstances (BINV- Q). NERLYNX is included (i) with or without fulvestrant and (ii) with or without trastuzumab / fulvestrant. This inclusion is described in a table entitled, " Emerging Biomarkers to Identify Novel Therapies for Patients with Stage IV (M1) Disease, " within the NCCN Practice Guidelines for Breast Cancer. Dose escalation of neratinib is included as an approach to improve the tolerability of neratinib in the treatment of metastatic HER2- positive breast cancer **. NERLYNX monotherapy is also included in the body of the NCCN Practice Guidelines for Cervical Cancer for use as a second- line or subsequent therapy for patients with recurrent or metastatic cervical cancer and a mutation in the HER2 gene. NERLYNX is included in CERV- F under the heading Useful in Certain Circumstances and designated as a category 2A treatment option. Use of NERLYNX in cervical cancer patients is outside the FDA- approved indication for NERLYNX and considered investigational, and we may not market or promote NERLYNX for these uses. Neratinib is also being investigated in an ongoing Phase 1 trial (NCT05372614) that is sponsored by the National Cancer Institute to evaluate the combination of neratinib and fam- trastuzumab deruxtecan (Enhertu) in patients with metastatic solid tumors. The Phase 1 trial includes patients with metastatic solid tumors harboring HER2- overexpression (immunohistochemistry 3), ERBB2 amplifications, or activating HER2 mutations. The primary objectives are to assess safety and tolerability of the combination, and the secondary objectives include evaluating pharmacokinetics, preliminary efficacy, and potential biomarkers of response** . Alisertib is an investigational reversible, ATP- competitive inhibitor that is designed to be highly selective for Aurora Kinase A. Inhibition of Aurora Kinase A leads to disruption of mitotic spindle apparatus assembly, disruption of chromosome segregation, and inhibition of cell proliferation. In clinical trials to date, alisertib had shown single agent activity and activity in combination with other cancer drugs in the treatment of many different types of cancers, including hormone receptor positive breast cancer, triple negative breast cancer, small cell lung cancer and head and neck cancer. The drug has also shown activity in previous clinical trials in peripheral T cell lymphoma and non- Hodgkin' s lymphoma. Prior to our licensing alisertib from Takeda the drug was tested in over 1, 300 patients who were treated across 22 company sponsored trials resulting in a large well characterized clinical safety database. We intend to pursue the development of alisertib in hormone receptor positive. HER2- negative, breast cancer as well as small cell lung cancer based on the prior clinical data that has been generated. We also plan to evaluate alisertib in biomarker focused populations where it has shown a higher degree of activity, such as patients with c- ~~myc~~ **Myc** amplification and RB1 loss / RB1 mutations, as we believe that this may provide a point of differentiation from the other drugs being developed in the treatment of these diseases. During 2023, we met with the FDA to discuss our alisertib clinical development plan in both proposed indications and discussed potential dosing schedules for alisertib **. Following comments from the FDA on the proposed clinical development plans, we initiated clinical trials for both small cell lung cancer and breast cancer in 2024 and are currently enrolling** . Alisertib in Small Cell Lung Cancer In a Phase II trial that was published in Lancet Oncology in 2015, alisertib was tested as a single agent in several cohorts of patients with solid tumors. These included small cell lung cancer as well as breast cancer. In small cell lung cancer, the study design involved the administration of alisertib to patients with small cell lung cancer who had previously received up to two prior cytotoxic regimens in the metastatic setting. Patients were administered alisertib monotherapy at a dose of 50 mg twice a day (" BID ") for seven days followed by a 14- day break. In patients with chemotherapy sensitive disease, alisertib resulted in a response rate of 19 % and a duration of response of 3. 1 months. For the patients with chemotherapy refractory disease or chemotherapy resistant disease, alisertib resulted in a response rate of 25 % and a duration of response of 4. 3 months. The main grade 3 or higher adverse events (" AEs ") seen in the trial were neutropenia, anemia, leukopenia and thrombocytopenia. Alisertib was also tested in a randomized Phase II trial of paclitaxel plus alisertib versus paclitaxel plus placebo in patients with second line small cell lung cancer, the results of which were published in the Journal of Thoracic Oncology in 2020. In the trial, alisertib was dosed at 40 mg BID for 3 weeks on days 1 – 3, 8 – 10, and 15 – 17 plus paclitaxel (60 mg / m2 intravenously on days 1, 8, and 15) whereas the comparator arm received placebo plus paclitaxel (80 mg / m2 intravenously on days 1, 8, and 15) in 28- day cycles. Randomization was stratified by type of relapse after primary treatment, based on the common definition for each type (with sensitive defined as relapsed greater than 90 but less than 180 days after primary treatment and resistant or refractory defined as relapsed less than or equal to 90 days after primary treatment). The protocol was initially written by the sponsor to record relapse type as the time from initial response. The protocol was corrected approximately midway through the trial to correct the stratification definition of relapse type after primary treatment so that relapses were recorded " from last administration of platinum- based chemotherapy, " which is in line with the NCCN treatment guidelines and clinical treatment practice rather than " from initial response. " To maintain balance, the primary end point of PFS was analyzed by using the original stratification definition of relapse type. However, a sensitivity analysis which used the corrected stratification definition was also performed. The trial also incorporated an extensive biomarker analysis with a

prespecified analysis of c- Myc expression and an exploratory, retrospective analysis of genetic alterations in circulating tumor DNA (“ ctDNA ”) with clinical outcome. The primary endpoint in the trial was PFS. For the intent to treat (“ ITT ”) population the hazard ratio using the original definition was 0. 77 with a p value of 0. 113. Using the corrected definition of relapse type, the hazard ratio was 0. 71 with a p value of 0. 038. For the patients with chemotherapy resistant or refractory relapse the hazard ratio was 0. 66 with a p value of 0. 037. For the ITT population the OS data showed a hazard ratio of 0. 87 with a p value of 0. 714 and using the corrected definition the hazard ratio was 0. 79 with a p value of 0. 209. Higher rates of grade 3 or higher AEs were seen in the alisertib arm for neutropenia, anemia and decreased neutrophil count. For the patients in the trial who were found to be positive for c- ~~myc~~ **Myc** expression by immunohistochemistry the hazard ratio in the trial was 0. 29 with a median PFS for the paclitaxel plus alisertib arm of 4. 64 months and a median PFS for the placebo plus paclitaxel arm of 2. 27 months. The trial also incorporated an analysis of patients with alterations in cell cycle genes including cyclin- dependent kinase 6 gene (CDK6), retinoblastoma- like 1 gene (RBL1), retinoblastoma- like 2 gene (RBL2), and retinoblastoma 1 gene (RB1). Of note RB1 mutations were the most ~~frequently~~ -- **frequent** mutation with approximately 60 % of the patients having RB1 mutations while CDK6, RBL1 and RBL2 mutations were found with very low frequency. For patients with cell cycles mutations (RB1, CDK6, RBL1 and RBL2), the PFS in the paclitaxel plus alisertib arm was 3. 68 months while the placebo plus paclitaxel arm was 1. 8 months and the hazard ratio was 0. 395 with a p value of 0. 003. The overall survival in this subgroup of patients was 7. 2 months for the alisertib arm and 4. 47 months for the placebo arm with a hazard ratio of 0. 427 and a p value of 0. 00085. Development plan. In the United States the incidence of small cell lung cancer is approximately 31, 000 to 33, 000 patients per year with approximately 17, 000 to 18, 000 deaths per year. There are two biomarkers of interest, c- ~~myc~~ **Myc** amplifications and RB1 mutations / deletions, that we intend to study with alisertib based on the previous clinical trial results which may provide differentiation from the other drugs in development. According to the published biomarker data from the alisertib clinical trial, approximately 72 % of small cell lung cancer patient samples had c- ~~myc~~ **Myc** amplifications and approximately 60- 80 % of small cell lung cancer patient samples had RB1 mutations. In August 2023, we announced that we had been notified by the FDA that we can proceed under our Investigational New Drug application (“ IND ”) with the clinical development of alisertib monotherapy for the treatment of patients with extensive stage small cell lung cancer ~~(“ SCLC ”)~~. Our Phase II trial ~~(~~ ALISertib in CAncer (ALISCA **™** - Lung1) Phase II trial (PUMA- ALI- 4201)) will enroll up to 60 patients with extensive stage small cell lung cancer who have progressed after first- line platinum- based chemotherapy and immunotherapy. Patients must provide tissue- based biopsies so that biomarkers can be analyzed. Alisertib will be dosed at 50 mg BID on days 1- 7 of every 21- day cycle. In February 2024 we announced that we initiated the Phase II ~~ALISCA~~ **ALISCATM** - Lung1 trial **. This study is ongoing and actively recruiting** . The primary endpoint of the trial **is** ~~will be~~ objective response rate with secondary endpoints of duration of response, disease control rate, **PFS** ~~progression free survival~~ and overall survival. We will **look** ~~also be looking~~ at each of these endpoints within selected pre- specified biomarker subgroups ~~as well as~~ to assess whether there is enhanced efficacy in any biomarker subgroup. We will ~~be performing~~ --- **perform** a biomarker analysis of the ALI- 4201 trial in parallel with the execution of the clinical trial. We plan to perform an initial interim analysis for the evaluation of the biomarkers as well as an evaluation of the efficacy. Based upon the outcomes of the study, we anticipate meeting with the FDA to explore the potential for an accelerated approval pathway for alisertib in small cell lung cancer. Alisertib in Breast Cancer In the same Phase II trial of alisertib monotherapy that was published in Lancet Oncology in 2015, alisertib was also tested in patients with HER2- negative, hormone receptor positive breast cancer, HER2- positive breast cancer and triple negative breast cancer. Patients were administered alisertib monotherapy at a dose of 50 mg BID for seven days followed by a 14- day break. In the cohort of patients with HER2- negative, hormone receptor positive breast cancer, treatment with alisertib resulted in a response rate of 23 % with a PFS of 7. 9 months. The main grade 3 / 4 AEs seen were neutropenia, leukopenia, stomatitis and fatigue. Alisertib was also tested in a randomized Phase II trial in hormone receptor positive, HER2- negative metastatic breast cancer patients that was presented at the San Antonio Breast Cancer Symposium in 2020 and published in JAMA Oncology in March 2023. In this trial alisertib was dosed at 50 mg BID on days 1- 3, 8- 10 and 15- 17 on a 28 day cycle while fulvestrant was dosed at its approved dose of 500 mg IM on days 1 and 15. The baseline characteristics from the trial were well balanced although a higher percentage of patients with prior chemotherapy given in the metastatic setting were present in the alisertib plus fulvestrant arm. Of note, patients were required to have been treated with prior fulvestrant as an inclusion criteria for the trial. The results from the trial showed a response rate of 19. 6 % in the alisertib alone arm and 20. 0 % in the alisertib plus fulvestrant arm. The median duration of response was 15. 1 months for the alisertib alone arm and 8. 5 months for the alisertib plus fulvestrant arm. The PFS was 5. 6 months in the alisertib alone arm and 5. 4 months in the alisertib plus fulvestrant arm. The main AEs seen in the trial were similar to the prior monotherapy trial with incidences of neutropenia, anemia, and decreases in white blood cells and lymphocytes seen. Alisertib was also tested in a randomized Phase II trial in hormone receptor positive, HER2- negative metastatic breast cancer and triple negative breast cancer patients, which was published in JAMA Network Open in 2021, in which patients were randomized to receive either paclitaxel plus alisertib or paclitaxel alone. In this trial alisertib was dosed at 40 mg BID on days 1- 3, 8- 10 and 15- 17 on a 28- day cycle while paclitaxel was dosed at 60 mg / m2 on days 1, 8 and 15 of a 28- day cycle. In the control arm paclitaxel was dosed at 90 mg / m2 on days 1, 8 and 15 of a 28- day cycle. The combination of paclitaxel plus alisertib resulted in a statistically significant improvement in PFS with a hazard ratio of 0. 56 and a p value of 0. 005. The median PFS in the paclitaxel plus alisertib arm was 10. 2 months and the median PFS in the paclitaxel alone arm was 7. 1 months. Treatment with paclitaxel plus alisertib resulted in a numerically higher but not statistically significant improvement in overall survival ~~with~~ **where** the median OS for the paclitaxel plus alisertib arm was 26. 3 months versus 25. 1 months for the single agent paclitaxel arm of the trial which resulted in a hazard ratio of 0. 89 and a p value of 0. 61. The standard of care for the first line treatment of hormone receptor positive, HER2- negative metastatic breast cancer in the United States is treatment with Cyclin- dependent kinases (CDK) 4 / 6 inhibitors (CDK 4 / 6 inhibitors). In the cohort of patients in the trial who were treated with CDK 4 / 6 inhibitors, the combination of paclitaxel plus alisertib resulted in a median

PFS of 13. 9 months while paclitaxel alone resulted in a median PFS of 5. 6 months. The hazard ratio was 0. 59 with a p value of 0. 19. In the cohort of patients with triple negative breast cancer, the combination of paclitaxel plus alisertib resulted in an improvement in PFS with a hazard ratio of 0. 35 and a p value of 0. 022. The median PFS in the paclitaxel plus alisertib arm was 9. 6 months and the median PFS in the paclitaxel plus placebo arm was 5. 7 months. Treatment with paclitaxel plus alisertib resulted in a higher but not statistically significant improvement in overall survival ~~with~~ **where** the median OS for the paclitaxel plus alisertib arm was 16 months versus 12. 7 months for the paclitaxel alone arm of the trial which resulted in a hazard ratio of 0. 51 and a p value of 0. 09. Higher rates of grade 3 or higher AEs were seen in the paclitaxel plus alisertib arm for neutropenia, leukopenia, diarrhea, mucositis and stomatitis. Archival tissue samples from patients enrolled in the clinical study were analyzed as part of a biomarker evaluation strategy. Of the 140 patients enrolled in the trial, 45 from the alisertib plus paclitaxel arm and 51 from the paclitaxel arm had sufficient tissue available for next generation sequencing, and 31 from the alisertib plus paclitaxel arm and 35 from the paclitaxel arm had enough for RNA sequencing / gene set enrichment analysis. The most frequently mutated genes were PIK3CA (45 %) and TP53 (44 %). No mutations were significantly associated with response or resistance to alisertib plus paclitaxel, including those in PIK3CA, TP53, AKT1, HER2, and CDH1. Increased MYC RNA expression was observed in tumors from patients who did not derive clinical benefit from paclitaxel alone (defined as PFS less than ~~6~~ **six** months) compared to those with benefit from paclitaxel alone (defined as PFS greater than or equal to ~~6~~ **six** months). Increased MYC RNA expression was not observed in patients who did not appear to benefit from alisertib plus paclitaxel. Elevated expression of genes involved in MYC activation and in unfolded protein response (a pro- survival mechanism) were enriched in alisertib plus paclitaxel responders compared to paclitaxel responders and were associated with poor response to paclitaxel alone. In 12 patients with exceptional response to alisertib plus paclitaxel (defined as PFS greater than or equal to 12 months), increased expression of genes involved in MYC activation and in epithelial to mesenchymal transition (a hallmark of cancer progression and metastasis) was observed in comparison to cancers from patients whose disease progressed within ~~6~~ **six** months of initiating alisertib paclitaxel (n = 11) or those with exceptional response to paclitaxel alone (n = 4). Development plan. In the United States the incidence of hormone receptor positive HER2- negative breast cancer is 40, 000 patients per year with 29, 700 deaths per year. There are two biomarkers of interest that we intend to study with alisertib, c- ~~myc~~ **Myc** amplifications and RB1 mutations / deletions. According to biomarker analyses from clinical trials, approximately 50 % of hormone receptor positive breast cancer tumors may have c- ~~myc~~ **Myc** amplifications and approximately 2- 9 % of hormone receptor positive HER2- negative breast cancer samples have RB1 mutations detected at the time of resistance to ~~cdk4~~ **CDK 4** / 6 inhibitors. Based on ~~the~~ our interactions with the FDA ~~in 2023~~, we ~~plan to initiate~~ **initiated** a Phase II trial of alisertib in combination with endocrine treatment (consisting of either anastrozole, exemestane, letrozole, fulvestrant or tamoxifen) in patients with chemotherapy- naïve HER2- negative, hormone receptor- positive metastatic breast cancer (ALISCA ™ - Breast1). Patients must have been previously treated with CDK 4 / 6 inhibitors and received at least two prior lines of endocrine therapy in the recurrent or metastatic setting to be eligible for the trial. ~~We plan to~~ **In November 2024, we announced that we** ~~initiate~~ **initiated** ~~this~~ **the Phase II ALISCATM- Breast1** trial ~~in~~**, and** the ~~second half of 2024~~ **study is actively enrolling patients** . The ~~ALISCA~~ **ALISCATM** - Breast1 trial is designed to dose patients with alisertib given at either 30 mg, 40 mg or 50 mg twice daily (BID) on days 1- 3, 8- 10 and 15- 17 on a 28- day cycle in combination with the endocrine therapy of the investigator' s choice. Patients must not have been previously treated with the endocrine treatment that will be given in combination with alisertib in the trial. Each dose level is expected to enroll up to 50 patients. Patients must provide blood samples and tissue- based biopsies so that biomarkers can be evaluated. The primary **objective is to determine the optimal alisertib dose level administered in combination with selected endocrine therapy to be used in future studies. The primary** efficacy end points ~~will~~ include objective response rate, duration of response, disease control rate and PFS. As a secondary objective, ~~the~~ we **will** ~~plan to~~ evaluate each of these efficacy endpoints within biomarker subgroups in order to determine whether any biomarker subgroup correlates with more favorable efficacy results, such as ~~though~~ **through** observed in preclinical and clinical studies in other cancers including breast cancer and small cell lung cancer. Pending the outcome of this ~~planned~~ study, we may then look to focus the future clinical development of alisertib in combination with endocrine therapy for patients with HER2- negative hormone receptor- positive breast cancer in patients with any potential biomarkers. Based on our interactions with the FDA, we believe that this trial design could find the optimal dose of alisertib in combination with endocrine therapy in patients with HER2- negative, hormone receptor- positive metastatic breast cancer, and pending sufficiently positive results, allow us to move into a pivotal Phase III trial. Once the optimal alisertib dose is identified, we plan to engage with global regulatory agencies regarding the design of a pivotal Phase III trial, which we anticipate will be a randomized trial of alisertib plus investigator' s choice endocrine therapy versus placebo plus investigator' s choice endocrine therapy in patients with chemotherapy naïve HER2- negative, hormone receptor- positive metastatic breast cancer. Clinical Testing of Our Drug Candidates Any drug candidates we seek to develop will require extensive pre- clinical and clinical testing to determine its safety and efficacy in the potential applications **before** ~~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 Regulation (Regulation (EU) No 536 / 2014 of April 16, 2014), and applicable national laws of the 27 EU member states. 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. Significant financial resources are invested in research, development and commercialization of new cancer products. We have faced and will likely continue to face considerable competition from major pharmaceutical, biotechnology and specialty cancer companies. Our competitors include, but are not limited to, Genentech, Novartis, Roche, Boehringer Ingelheim, Lilly, Amgen, Daiichi Sankyo, Jazz and Seagen. Amgen, Daiichi Sankyo and Jazz are developing their drugs for the treatment of small cell lung cancer. All of the other 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 aware of the DESTINY- Breast11 neoadjuvant trial and DESTINY- Breast05 adjuvant trial of trastuzumab deruxtecan in early stage HER2- positive breast cancer, as well as the CompassHER2 RD trial of tucatinib in early stage HER2- positive breast cancer.** In addition, we are also competing with academic institutions, governmental agencies and private organizations that are conducting research in the field of cancer. We are a small biotechnology company with a limited history of sales, marketing, operations and commercial manufacturing. Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early ~~-~~stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and enrolling subjects for our clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. We could see a reduction or elimination of our commercial opportunity if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we or our collaborators may develop. Our competitors also may obtain FDA or foreign regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we or our collaborators are able to enter the market. We anticipate that we will continue to face significant competition in the ongoing commercialization of NERLYNX and the commercialization of any of our drug candidates that receive marketing approval. Our competition will be determined by several factors including but not limited to the specific indications approved, the timing of any approvals as well as competitive activity and entrants within this space. We expect that competition among products approved for sale will be based on various factors, including safety, efficacy, pricing and contracting, patient support services, access and reimbursement, formulary and pathway adoption as well as patent position. Sales and Marketing We currently have an oncology sales force in the United States comprised of approximately ~~38~~ **35** sales specialists, ~~8~~ **three** clinical nurse educators ~~and four~~ **, two** strategic account managers and one national account director who are focused on promoting NERLYNX to oncologists and the oncology care team. This sales force is supported by an experienced leadership team consisting of ~~6~~ **six** regional business leaders and a VP of sales. In addition, the broader commercial team is comprised of experienced professionals in marketing, training, sales operations, global product strategy as well as access and reimbursement. **Our** ~~In addition, our~~ commercial infrastructure includes capabilities in manufacturing, regulatory, quality control, and compliance. It is also supported from a clinical ~~expertise~~ and cancer landscape perspective by our medical affairs group. We launched NERLYNX in the United States in July 2017 with the goal of establishing NERLYNX as the standard of care for the extended adjuvant treatment of adult patients with early stage HER2- positive breast cancer to follow adjuvant trastuzumab- based therapy. In Feb 2020, NERLYNX was also approved in the United States 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 that the key commercial priorities ~~to achieve~~ for NERLYNX include: • Educating healthcare providers about the evolving clinical data for NERLYNX and its ability to reduce the risk of recurrence in the extended adjuvant setting for ~~woman~~ **patients** battling HER2- positive breast cancer; • Educating HER2- positive breast cancer patients about the risks of recurrence and empowering them to ask their MDs if NERLYNX is an appropriate option for them; • Removing access barriers by ensuring broad insurance coverage; and • Providing patients with appropriate co- pay support as well as tools and resources to better maintain persistency and compliance. In the United States, we sell our products through a specialty pharmacy network and special distributor network. The specialty pharmacy network sells directly to patients and consists of Acaria Health, Accredo, CVS, ONCO 360, Optum ~~/ Diplomat~~ and Biologics. Our specialty distributor network sells to hospitals, physician practices and other sites of care and consists of McKesson, ASD / Oncology Supply, Cardinal Health and DMS Pharmaceutical Group. International Outside the United States, we seek to enter into exclusive sub- license agreements with third parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved. 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 ago. In December 2021, NERLYNX (neratinib) was included in the updated National Reimbursement Drug List (“ NRDL ”) by the China National Healthcare Security Administration 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. We continue to pursue commercialization of NERLYNX in Europe and other countries outside the United States, where approved. The following table shows the HER2- positive breast cancer approvals for NERLYNX by disease and country: Extended adjuvant Metastatic United States July 2017 United States February 2020 European Union August 2018 Argentina January 2021 Australia March 2019 Peru March 2021 Canada July 2019 Chile May 2021 Argentina August 2019 Canada June 2021 Hong Kong October 2019 Taiwan October 2021 Singapore November

2019 Israel July 2022 Switzerland March 2020 Ecuador August 2022 Brunei April 2020 Singapore September 2022 China April 2020 Colombia March 2023Chile April 2020 Malaysia September **2023New** ~~2023 New~~ Zealand June 2020 **Mexico October** ~~Taiwan~~ **2023Taiwan** June 2020 **Brazil May** ~~Ecuador~~ **2024Ecuador** July 2020 **Thailand December 2024** Malaysia July 2020 Peru March 2021 Macau August 2021 South Korea October 2021 Brazil December 2021 Mexico January 2022 Philippines June 2022 Israel July 2022 South Africa January 2023 Morocco February 2023 **UAE September 2023 Syria January 2024 Saudi Arabia July 2024 Algeria July 2024 Turkey November 2024 Thailand December 2024** We currently have sub- licenses in each of these regions with third parties that are commercializing NERLYNX in their respective geography. Intellectual Property and License Agreements Neratinib Patent Portfolio We hold a worldwide exclusive license under our license agreement with Pfizer, as amended (the " Pfizer Agreement ") to 21 granted U. S. patents and ~~four~~ **three** 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~~ **on October 8,** 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 latter 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, based on our existing neratinib patent portfolio, that covers 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. U. S. Patent No. 7, 399, 865 Patent Term Extension (PTE) Certificate **was** issued on November 19, 2021. 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 combination 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 ~~are~~ potentially 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 ~~2022~~ **2024** , marketing approval for neratinib was obtained in Argentina, Brazil, Brunei, Canada, Chile, China, Ecuador, Hong Kong, Israel, Malaysia, Mexico, Singapore ~~and~~ **,** Taiwan **, Brazil and Thailand** . 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. We are pursuing patent term extension in the form of patent term adjustment (PTA), in market approved jurisdictions where PTA is available. Where PTA requests require proceedings in a court setting, there is no guarantee that such PTA requests will be granted. 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 Supplemental Protection Certificate applications, ~~five~~ **seven** have been granted, one is ~~pending grant~~ **undergoing appeal proceedings** , ~~four~~ **six** have been abandoned **, five proceedings have been stayed,** and the remaining **six** 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. One European divisional application, namely EP15188350. 1, was granted with the European patent number EP3000467 on March 1, 2023. Oppositions against EP3000467 were filed by Hexal AG (" Hexal ") on November 3, 2023, by Alfred E. Tiefenbacher (GmbH & Co. KG) on November 28, 2023 and by Generics ~~(~~ (UK ~~)~~) Limited **(" Generics ")** on December 1, 2023. EP3000467 is used as the basic patent for Supplementary Protection Certificate applications for the EMA- approved NERLYNX ® product **, 17 of which have been granted, three proceedings have been stayed, and eleven are in active prosecution** . **The patentee** ~~Responses~~ **response** to the ~~notices~~ **notice** of opposition **was** ~~need to be~~ filed ~~by~~ **on** April 15, 2024 **, following which, all three opponents filed additional arguments in reply to the patentee' s submission. On February 6, 2025, we filed our response to the summons to attend oral proceedings. Oral proceedings are currently scheduled for April 9, 2025** . One European divisional application is pending in the same family, namely EP 23157078. 8. ~~Substantive examination thereof has not yet commenced~~ **A response to the European Search Opinion (ESO) for this application was filed February 14, 2024** . On October 6, 2017, Hexal also filed an Opposition against 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, the Board of Appeal of the European Patent Office rejected the claims as granted and the pending auxiliary request during the oral hearing of November 16, 2022. Before issuance of a decision, we withdrew approval of the text in which the patent was granted and the pending auxiliary request, thereby revoking the patent and concluding the appeal. A divisional application, EP16203986. 1 was granted with the patent number EP3175853 on November 1, 2023. **This patent was also opposed by Sandoz AG on July 2, 2024. The patentee' s response was filed on December 12, 2024. On December 19, 2024, Sandoz AG requested the opposition division to delay issuance of their preliminary opinion by two months since they intend to respond to the patentee' s submission.** A divisional application, EP23206402. 2, remains pending in this family. ~~Claims for this pending divisional need to be filed by January 8, 2024.~~ Substantive examination ~~thereof~~ has ~~not yet~~ commenced **and a response to the European Search Opinion (ESO) is due by May 20, 2025** . On May 21, 2020, Dr. Richard Cooke at the firm Elkington and Fife LLP filed an Opposition against 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. An oral hearing was held on April 6, 2022, wherein the patent has been maintained in amended form. The Interlocutory Decision of the Opposition Division was issued on July 25, 2022. Hexal, has not appealed the decision within the prescribed time and the Interlocutory Decision became final. **A** ~~There are two pending~~ divisional ~~applications~~ **application for** ~~, namely~~ EP19154710. 8 **has been granted as EP3566697,** and EP22169771. 7 **has** ~~, wherein the latter~~ received ~~Third Party Observations~~ **a decision to grant, taking effect** on ~~December 1~~ **March 5** , ~~2023~~ **2025** . 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. Alisertib Patent Portfolio We hold a worldwide exclusive license under our license agreement with Takeda (the " Takeda Agreement "), to ~~20~~ **22** granted U. S. patents and ~~5~~ **five** pending U. S. patent applications, as well as foreign counterparts thereof, and other patent applications and patents claiming priority ~~therefrom~~ --- **thereof** for a total of approximately ~~363~~ **368** foreign patents and patent applications to develop and commercialize alisertib. We have a license to issued U. S. patents that include species claims and genus claims to the composition of matter of alisertib which are set to expire in 2029 and 2027, respectively, not including any extension for Hatch- Waxman exclusivity. We also have issued U. S. patents for the use of alisertib in combination with certain other agents in the treatment of certain proliferative disorders, small- cell lung cancer and breast cancer, which are currently set to expire in 2032, 2033 and 2034, respectively, not including any extension for Hatch- Waxman exclusivity. We plan to pursue additional patents in and outside the United States, based on our existing alisertib patent portfolio, that covers alisertib composition, formulations, combinations and uses thereof, and additional therapeutic uses of alisertib. In addition, we will pursue patent protection for any new discoveries or inventions made in the course of our development of alisertib. 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 drug candidates and any future drug 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 Agreements Pfizer 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. 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~~ **exceeded** 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 (“ 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 (the “ 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 accrued 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. Takeda License Agreement In September 2022, we entered an exclusive license agreement with Takeda to license from Takeda the worldwide right to research, develop, commercialize and otherwise exploit alisertib, also referred to as MLN- 8237, a selective, small- molecule, orally administered inhibitor of ~~aurora~~ **Aurora** ~~kinase~~ **Kinase** A. Under the terms of the Takeda Agreement, we assumed sole responsibility for the global development and commercialization of alisertib. We paid Takeda an upfront license fee of $ 7 **. 0** million in October 2022 and **Takeda** is eligible to receive potential future milestone payments of up to $ 287. 3 million upon our achievement of certain regulatory and commercial milestones during the term of the exclusive license agreement, as well as tiered royalty payments for any net sales of alisertib. Under the Takeda Agreement, we must use commercially reasonable efforts to develop and commercialize one product containing alisertib in specified major- market countries. We may terminate the Takeda Agreement at will at any time upon specified advance notice. Each party may terminate the Takeda Agreement if the other party fails to cure any material breach of the Takeda Agreement by such other party within a specified time period. In addition, each party may terminate the Takeda Agreement following the other party’ s bankruptcy, insolvency, reorganization, receivership, dissolution, liquidation or similar events. The Takeda Agreement contains other customary clauses and terms as are common in similar agreements in the industry. Sub- License Agreements The following summary describes our material sub- license agreements. Because the following is only a summary, it does not contain all of the information that may be important to you. For a complete description, you should refer to each of these agreements, copies of which have been filed as exhibits to this Annual Report on Form 10- K. Specialised Therapeutics Agreement On November 20, 2017, we entered into a sub- license agreement (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 (the " Medison Agreement "), with Medison Pharma Ltd. (" 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 (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 (the " Pint Agreement "), with Pint Pharma International SA (" 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 (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 (the " Knight Agreement "), with Knight Therapeutics, Inc. (" 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 (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 (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 (the " Pierre Fabre Agreement "), with Pierre Fabre Medicament SAS (" 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 (the " Pierre Fabre Territory "). On November 25, 2019, we entered into a license amendment (the " First Pierre Fabre Amendment "), with Pierre Fabre to extend the Pierre Fabre Territory to the Middle East, South Africa, Sudan and Turkey (as extended, 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 (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 (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 support commercialization of NERLYNX and development of our drug candidates, including alisertib, rather than diverting resources to establish our own manufacturing facilities. While our drug candidates were developed by Pfizer and Takeda, both the drug substance and drug product are manufactured by third- party contractors. We are currently using third- party contractors to manufacture, supply, store and distribute our neratinib products (including NERLYNX) in clinical trials and commercial quantities as well as for alisertib in clinical trials. Should alisertib or 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. 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 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, certain of which must be conducted in accordance with the FDA' s GLP requirements and other applicable regulations; • submission to the FDA of an 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 potential inspection of clinical trial sites to assess compliance with GCP; 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. Therefore, submission of an IND may not necessarily 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 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 in order to establish the risk / benefit profile of the drug and provide an adequate basis for product labeling. 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 drug 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 may be waived in circumstances, such as where the drug is approved for an orphan- designated ~~indications~~ **indication**, or for the

first NDA submitted by a qualifying small business. 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. Once filed, 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~~ **10** 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 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 API 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 or a 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. Orphan Drug Designation. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200, 000 individuals in the United States or, if it affects more than 200, 000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or inability to manufacture the product in sufficient quantities. The designation of such drug also entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user- fee waivers. However, competitors, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan exclusivity also could block the approval of a competing product for seven years if a competitor obtains approval of the " same drug, " as defined by the FDA, or if a drug candidate is determined to be contained within the competitor' s product for the same disease or condition. In addition, if an orphan designated product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan exclusivity. 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 drug candidate and the specific

indication for which it is being studied. The sponsor of a fast track drug candidate has opportunities for more frequent interactions with the FDA review team during development. With regard to a fast track- designated drug 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 drug 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 drug candidate can receive breakthrough therapy designation if preliminary clinical evidence indicates that the drug 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 I and an organizational commitment to expedite the development and review of the drug candidate, including involvement of senior managers. Any drug candidate submitted to the FDA for approval, including a product with a fast track designation **or breakthrough therapy 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 drug 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~~ **10** months for review of new molecular entity NDAs under its current PDUFA review goals. **Depending on the design of the applicable clinical studies,** ~~Drug~~ **drug** ~~products~~ **candidates** intended for serious or life threatening conditions may also be eligible for accelerated approval upon a determination that the drug 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 generally requires that a sponsor of a drug receiving accelerated approval perform adequate and well- controlled confirmatory clinical trials to verify or characterize the anticipated effect on irreversible morbidity or mortality or other clinical benefit and may require that such confirmatory trials be **well** underway prior to granting any accelerated approval. 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 drug 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 and their subcontractors must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. 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. **Marketing exclusivity** 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 (“ 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 non- patent 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 are subject to a variety of foreign regulations governing, among other things, clinical trials, marketing authorization **(“ MA ”)** , commercial sales and distribution of our products. The foreign regulatory approval process includes all of the risks associated with FDA approval set forth above, as well as additional country- specific regulation. 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. Approval by one regulatory authority does not ensure approval by regulatory authorities in other jurisdictions. The approval process varies from country to country, can involve additional testing beyond that required by FDA, and may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement also vary greatly from country to country. Non- clinical studies and clinical trials As in 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 (pharmaco- toxicological) studies must be conducted in compliance with the principles of GLP as set forth in EU Directive 2004 / 10 / EC (unless otherwise justified for certain particular medicinal products, e. g., radio- pharmaceutical precursors for radio- labeling purposes). 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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (“ 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 member states, 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 EU 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 EU Clinical Trials Directive required a separate clinical trial application (“ CTA ”) to be submitted in each EU member state in which the clinical trial takes place, 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 for multi- center trials. 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 **ended on** ~~. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to~~ January 31, ~~2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31,~~ 2025 ~~. After this date~~ , **and** all clinical trials (~~including those which~~ **and related applications)** are **now fully** ~~ongoing) 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 order to market our drug candidates in the EU and many other foreign jurisdictions, we must obtain separate regulatory approvals. More concretely, in the EU, medicinal drug candidates can only be placed on the market after obtaining a ~~marketing authorization (“~~ MA ~~”)~~. To obtain regulatory approval of a ~~drug~~ **product** candidate under EU regulatory systems, we must submit **an** ~~a MA application (“~~ 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 drug 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 drug 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 (“ 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 EU member states assess the risk- benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. MAs 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~~ **an** MAA by the EMA is 210 days. In exceptional cases, the CHMP might perform an accelerated review of ~~a~~ **an** 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 United States. 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~~ **an** 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, in the EU, new products authorized for marketing (“ reference products ”) generally receive eight years of data exclusivity and an additional two years of market exclusivity upon MA. If granted, the data exclusivity period 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~~ **eight** 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 market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until ~~ten~~ **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~~ **eight** 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. Orphan Medicinal Products The criteria for designating an “ orphan medicinal product ” in the EU are similar in principle to those in the United States. A medicinal product can be designated as an orphan if its sponsor can establish that: (1) the product is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition (2) either (a) such condition affects not more than five in 10, 000 persons in the EU when the application is made, or (b) the product, without the benefits derived from the orphan status, would not generate sufficient return in the EU to justify the necessary investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition. Orphan designation must be requested before submitting an MAA. An EU orphan designation entitles a party to incentives such as reduction of fees or fee waivers, protocol assistance, and access to the centralized procedure. Upon grant of ~~a~~ **an** MA, orphan medicinal products are entitled to ~~ten~~ **10** years of market exclusivity for the approved indication, which means that the competent authorities cannot accept another MAA, or grant ~~a~~ **an** MA, or accept an application to extend ~~a~~ **an** MA for a similar medicinal product for the same indication for a period of ~~ten~~ **10** years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed pediatric investigation plan (“ PIP ”). No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan

designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The orphan exclusivity period may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for which it received orphan destination, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity or where the prevalence of the condition has increased above the threshold. Additionally, MA may be granted to a similar product for the same indication at any time if (i) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (ii) the applicant consents to a second orphan medicinal product application; or (iii) the applicant cannot supply enough orphan medicinal product. 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~~ **an** MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance (" QPPV ") who is responsible for the establishment and maintenance of that system, and oversees the safety profiles of medicinal products and any emerging safety concerns. 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 that apply to the conduct of clinical trials, manufacturing approval, MA of medicinal products and marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti- corruption or with other applicable regulatory requirements 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 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. Further, to the extent that any of our drug 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. Brexit and the Regulatory Framework in the United Kingdom ~~Since~~ **Following** the end of the Brexit transition period on January 1, 2021, ~~Great Britain~~ **and the implementation of the Windsor Framework on January 1, 2025, the United Kingdom** (**" UK "** ~~England, Scotland and Wales~~) ~~has~~ **is** not **generally** ~~been directly~~ subject to EU laws **in respect** ~~, however under the terms~~ of **medicines** ~~the Ireland / Northern Ireland Protocol, EU laws generally apply to Northern Ireland~~ . The EU laws that have been transposed into United Kingdom law through secondary legislation remain applicable in ~~Great Britain,~~ **the UK;** however, new legislation such as the **(** EU **)** CTR is not applicable in Great Britain. Under the Medicines and Medical Devices Act 2021, the Secretary of State or an ' appropriate authority' has delegated powers to amend or supplement existing regulations in the area of medicinal products and medical devices. This allows new rules to be introduced in the future by way of secondary legislation, which aims to allow flexibility in addressing regulatory gaps and future changes in the fields of human medicines, clinical trials and medical devices. Since January 1, 2021, the Medicines and Healthcare products Regulatory Agency (" MHRA ") **is** ~~, has been~~ the UK' s standalone medicines and medical devices regulator. As a result of the **Ireland /** Northern Ireland protocol, different rules **applied** ~~will apply~~ in Northern Ireland than in England, Wales, and Scotland, together, Great Britain (" GB ") ~~, broadly~~ , **which** ~~Northern Ireland will continue~~ **continued** to follow the EU regulatory regime ~~, but its national competent authority will remain the MHRA~~ . **However** ~~On February 27~~ , ~~2023, the UK Government and the European Commission reached a political agreement~~ on **January 1, 2025, a new arrangement called** the " Windsor Framework " ~~which will revise the~~ **came into effect and reintegrated** Northern Ireland ~~protocol in order to address some of the perceived shortcomings in its operation. Under the changes, Northern Ireland will be reintegrated~~ under the regulatory authority of the MHRA with respect to medicinal products. The Windsor Framework **removes EU licensing processes and EU labelling and serialization requirements in relation to Northern Ireland and introduces a** ~~was approved by the European Union- United Kingdom Joint Committee on March 24, 2023, so the~~ UK **- wide licensing process for** ~~government and the EU will enact legislative measures to bring it into law. On June 9, 2023, the MHRA announced that the~~ medicines aspects of the Windsor Framework will apply..... an application for a new GB MA . The UK regulatory framework in relation to clinical trials **is governed by the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, which** is derived from existing EU legislation (as implemented into UK law, through secondary legislation). On January 17, 2022, the MHRA launched an eight- week consultation on reframing the UK legislation for clinical trials which aimed to streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk

proportionality, and promote patient and public involvement in clinical trials. The MHRA **published its** ~~responded to the~~ consultation **outcome** on March 21, 2023 ~~and confirmed~~ **, confirming** that it would bring forward changes to the legislation. The ~~final legal texts introduced by the UK Government~~ **resulting legislative amendments, which are yet to be published,** will ultimately determine the extent to which the UK clinical trials framework aligns with or diverges from the (EU) CTR **aspects of the Windsor Framework will apply from January 1,2025.The MHRA has introduced changes to national licensing procedures,including procedures to prioritize access to new medicines that will benefit patients,including a 150- day assessment and a rolling review procedure** .All existing EU MAs for centrally authorized products were automatically converted or grandfathered into UK MAs,effective in GB (only),free of charge on January 1,2021,unless the MA holder opted-out. ~~Under the terms of the Windsor Framework,these MAs became valid for the whole of the UK from January 1,2025.~~ In order to use the centralized procedure to obtain ~~an~~ **a** MA that will be valid throughout the EEA,companies must be established in the EEA.Therefore,since Brexit,companies established in the UK can no longer use the EU centralized procedure and instead an EEA entity must hold any centralized MAs.In order to obtain a UK MA to commercialize products in the UK,an applicant must be established in the UK and must follow one of the UK national authorization procedures or one of the remaining post- Brexit international cooperation procedures **to obtain** ~~.Applications are governed by the Human Medicines Regulations (SI 2012 / 1916) and~~ **an** ~~are made electronically through~~ **MA to commercialize products in** the **UK** ~~MHRA Submissions Portal~~ . ~~The MHRA~~ **A new international recognition framework** has **been in place from** ~~introduced changes to national licensing procedures,including procedures to prioritize access to new medicines that will benefit patients,a 150- day assessment (subject to clock- stops) and a rolling review procedure.In addition,since~~ January 1,2024, **whereby** the MHRA ~~may rely~~ **will have regard to decisions on the approval of MAs made by the EMA and certain other regulators when determining an application for a new GB MA** . 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. Coverage and Reimbursement In the United States and internationally, sales of NERLYNX and any other product (s) 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 limits or deny coverage and reimbursement for our drug candidates, in whole or in part. In many countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. In the EU, governments influence the price of products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Member states are free to restrict the range of pharmaceutical products for which their national health insurance systems provide reimbursement, and to control the prices and reimbursement levels of pharmaceutical products for human use. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. Member states may approve a specific price or level of reimbursement for the pharmaceutical product, or alternatively adopt a system of direct or indirect controls on the profitability of the company responsible for placing the pharmaceutical product on the market, including volume- based arrangements, caps and reference pricing mechanisms. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular product to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. The downward pressure on healthcare costs in general, particularly prescription products, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low - priced markets exert a commercial pressure on pricing within a country. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower. 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. This legislation could increase the levels of discounts and rebates paid to federal and state government entities and significantly impact our ability to generate revenues. 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 (the " ACA "), enacted in March 2010, substantially changed the way healthcare is financed by both governmental and private insurers. Among ~~the~~ **other** provisions ~~of ,~~ the ACA **included** ~~, 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 ~~; • 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. **Thus, the ACA will remain in effect in its current form.** 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, led to reductions of Medicare payments to providers, which will remain in effect through 2032, 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, the American Rescue Plan Act of 2021 was signed into law, which eliminated the statutory Medicaid drug rebate cap, beginning January 1, 2024. The rebate was previously capped at 100 % of a drug' s average manufacturer price. Most significantly, in August 2022, **President Biden signed** the Inflation Reduction Act of 2022 **(“** ~~, or the~~ IRA **”)** ~~, was signed~~ into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare ~~(beginning in 2026)~~, with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); **redesigns the Medicare Part D benefit (beginning in 2024);** and replaces the Part D coverage gap discount program with a new **manufacturer** ~~discounting~~ --- **discount** program (beginning in 2025). **CMS** ~~The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as~~ **has** ~~opposed to regulation,~~ **published the negotiated prices** for the initial **10 drugs** ~~years. On August 29~~, **which will first be effective in** ~~2023~~ **2026** , ~~HHS announced~~ **and has published** the list of the ~~first ten~~ **subsequent 15** drugs that will be subject to ~~price negotiations~~ - **negotiation. The IRA permits the Secretary of the Department of Health and Human Services (“ HHS ”) to implement many of these provisions through guidance, as opposed to regulation, for the initial years** . HHS has ~~issued~~ and will continue to issue **and update** guidance **as these programs are** ~~implementing~~ **implemented** ~~the IRA~~ , although the Medicare drug price negotiation program is currently subject to legal challenges. **The** ~~While the~~ impact of the IRA on **us** ~~our business~~ and the pharmaceutical industry cannot yet be fully determined, ~~it~~ **but** is likely to be significant **. Under the IRA manufacturer discount program that replaced the coverage gap discount program as of January 1, 2025, manufacturers must give a 10 percent discount on Part D drugs in the initial coverage phase, and a 20 percent discount on Part D drugs in the so- called “ catastrophic phase ” (the phase after the patient incurs costs above the initial phase out- of- pocket threshold, which will be $ 2, 000 beginning in 2025). The IRA allows the 10 and 20 percent discounts to be phased in over time for certain drugs for “ specified manufacturers. ” In April 2024, CMS informed us that we are deemed a specified small manufacturer and the discount will be phased in over several years and will increase over time. We are continuing to evaluate the potential impact of this status on our future revenues. NERLYNX is reimbursed under Medicare Part D, and the reimbursement amount will be impacted by the 10 and 20 percent discounts under the IRA' s new discounting program (as noted above). We anticipate that these increased discounts will impact NERLYNX revenues over time, while also having an industry- wide impact on the patient out of pocket costs of Part D drugs. The impact on NERLYNX revenues could be offset because the IRA' s redesign of certain Part D components, some of which went into effect in 2024, resulted in an increase in the number of patients able to afford this therapy. The amount of the offset, if any, is inherently uncertain and difficult to predict. The IRA manufacturer discount program also increases financial obligations of Part D prescription drug plans with respect to beneficiaries in the catastrophic coverage phase. This may incentivize Part D prescription drug plans to seek greater price concessions from us in order to include NERLYNX on their formularies** . The cost of prescription pharmaceuticals in the United States continues to be 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. In the United States, individual states have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing. These actions include but are not limited to price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures. In some cases, these actions have been 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 EU, potential reductions in prices and changes in reimbursement levels could be the result of different factors, including reference pricing systems, parallel distribution and parallel trade. It could also result from the application of external reference pricing mechanisms, which consist of arbitrage between low- priced and high- priced countries. Reductions in the pricing of our medicinal products in one EU member state could affect the price in other EU member states and, thus, have a negative impact on our financial results. Health Technology

Assessment (“ HTA ”) of medicinal products in the EU is an essential element of the pricing and reimbursement decision-making process in a number of EU member states. The outcome of HTA has a direct impact on the pricing and reimbursement status granted to the medicinal product. A negative HTA by a leading and recognized HTA body concerning a medicinal product could undermine the prospects to obtain reimbursement for such product not only in the EU member state in which the negative assessment was issued, but also in other EU member states. In 2011, Directive 2011 / 24 / EU was adopted at the EU level. This Directive establishes a voluntary network of national authorities or bodies responsible for HTA in the individual EU member states. The network facilitates and supports the exchange of scientific information concerning HTAs. Further to this, in December 2021, Regulation No 2021 / 2282 on HTA, amending Directive 2011 / 24 / EU, was adopted. **The** ~~While the~~ Regulation entered into force in January 2022 **and has been applicable since** ~~, it will only begin to apply from~~ January 2025 ~~onwards~~ , with ~~preparatory and implementation- related steps to take place in the interim. Once applicable, it will have a~~ phased implementation ~~depending~~ **based** on the ~~concerned~~ **type of product, i. e. oncology and advanced therapy medicinal** products **as of 2025, orphan medicinal products as of 2028, and all other medicinal products by 2030** . The Regulation intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and provide the basis for cooperation at the EU level for joint clinical assessments in these areas. It will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the highest potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non- clinical (e. g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. In the future, there may continue to be additional proposals relating to the reform of the U. S. 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~~ **aged** 65 and over as well as those with certain disabilities. As a condition of having federal funds being made available for 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 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 ”) **that** ~~, 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 **a revised regulation implementing** 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 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 **reporting** requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information **. Some states have enacted legislation creating so- called prescription drug affordability boards, which ultimately may attempt to impose price limits on certain drugs in these states** . 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 to prescribe 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. In addition to the FDA, a company can be subject to legal claims from other governmental agencies and private parties relating to marketing practices such as the Federal Trade Commission (" FTC "), competitors, patients, and other third parties. 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, false claims 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. Violations of these 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. There are also state and foreign law and regulations 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. These laws and regulations may differ from one another in significant ways, thus further complicating compliance efforts. For instance, in the EU, many EU member states have adopted specific anti- gift statutes that further limit commercial practices for medicinal products, in particular vis- à- vis healthcare professionals and organizations. Additionally, there has been a recent trend of increased regulation of payments and transfers of value provided to healthcare professionals or entities and many EU member states have adopted national " Sunshine Acts " which impose reporting and transparency requirements (often on an annual basis), similar to the requirements in the United States, on pharmaceutical companies. Certain countries also mandate implementation of commercial compliance programs or require disclosure of marketing expenditures and pricing information. Violation of any of such laws or any other governmental regulations that apply may result in penalties, including, without limitation, significant administrative, civil and criminal penalties, damages, fines, disgorgement, additional reporting obligations and oversight if a manufacturer becomes subject to a corporate integrity agreement or other agreement to resolve allegations of non- compliance with these laws, the curtailment or restructuring of operations, exclusion from participation in governmental healthcare programs and imprisonment. 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. 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 (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 Employees As of December 31, ~~2023~~ **2024**, our workforce consisted of ~~185~~ **172** full- time employees. Throughout ~~2023~~ **2024**, the size of our employee population was fairly consistent, but ending with lower headcount at the end of the year due to reorganization **/ efficiency** efforts and employee attrition. Our employee population consists of a field- based commercial team, working from ~~a~~ home ~~office~~ **offices** and visiting customers across the country, employees **aligned with** ~~reporting out of~~ our two offices in the United States- Los Angeles, ~~CA~~ **California** and South San Francisco, ~~CA~~ **California** – and **the majority of non- field sales** employees working remotely from home on a consistent basis. For our office- based employees, during the latter part of 2022, **we** adopted a virtual work environment, allowing functional management and employees to determine when working virtually is more efficient and productive, and when in- office collaboration is beneficial. We are an equal opportunity employer and believe strongly in hiring and maintaining a diverse, equitable, and inclusive workforce. This is reflected in our numbers with our total workforce being approximately ~~50~~ **49** % women and ~~36~~ **37** % ethnically diverse. The following table summarizes our workforce by location for the years ended December 31, ~~2023~~ **2024** and December 31, ~~2022~~ **2023**: December 31, ~~2023~~ **2024** December 31, ~~2022~~ **2023** Los Angeles South San Francisco Field & Remote We believe that the safety and health of our employees and their families ~~is~~ **are** 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. Our financial, ~~medical, and mental~~ health **and wellness** benefits are designed to ~~help~~ **assist** employees ~~through crisis~~ **with financial planning**, **preventative health care,** and ~~we recently expanded our offerings~~ **support when unexpected circumstances arise. We continue** to ~~create appropriate "~~ **support employee wellbeing,** work **flexibility, and** ~~from home " conditions for those employees that are in field positions or choose not to~~ work ~~in~~ **efficiency by offering** the **following** ~~office to include~~: • **a robust offering of benefit options** ~~ergonomic webinars, 1x1 evaluations, and reimbursement for ergonomic equipment~~; • ~~phone and internet subsidies~~ **periodic reminders of our benefit options to our employees**; • ~~purchasing additional IT equipment~~ **a Lifestyle Spending Account to support employee wellness** and ~~office supplies~~ **fitness activities**; • ~~increasing communications related~~ **programming, including hosting a company- wide " Wellness Week " and " Walking Challenges "** to **motivate** ~~our~~

~~free Employee~~ **employees to engage with each other for increased physical fitness opportunities** ~~Assistance Plans, work / life assistance programs, and mental health benefits~~ ; • ~~professional resiliency coaching~~ **ergonomic support in the form of training opportunities, 1: 1 evaluations, and providing ergonomically compatible equipment when necessary** ; **and** • ~~subsidized~~ **subsidies** ~~subscriptions to ClassPass —~~ **for mobile devices and internet** access ~~to fitness, wellness, and mindfulness classes; and • hosting a virtual fitness challenge to inspire employees to be more active.~~ 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~~ **salaries** and cash target ~~bonus~~ **bonuses** ~~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, mental health services, life insurance, paid time off and family leave, 401 (k) match, fertility benefits, fitness / wellness 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 **and achieve** . 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. 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. **In addition, we offer an Educational Reimbursement Program to assist employees who want to further their educations.** Communication is critical in our ability to continuously enhance our company culture and create a more inclusive environment. ~~The implementation and distribution of~~ **We continue to publish a** quarterly ~~company newsletters~~ **newsletter** ~~have allowed us~~ to share **interesting** ~~what is important~~ and ~~impactful to us~~ **useful information through our involvement in cancer- related conferences and causes, such** as ~~a business~~ **Breast Cancer Awareness Month** . ~~It~~ **We** also ~~allows for us~~ **introduce new employees** to **the organization in our Welcome to Puma section, and profile existing employees in our Get Connected section, where we** share ~~stories~~ **information about their roles, motivations to be with Puma, backgrounds,** and **interests. In addition, we include information about upcoming employee** events ~~that have affected our~~ **and benefit opportunities, as well as previous events like** ~~employees~~ **employee team building** and **Wellness Week participation** ~~co- workers across the country on both a personal and professional level~~. We ~~hold~~ **conduct** town ~~halls~~ **hall meetings** ~~with our leaders~~ to ~~speak~~ **share information** with employees about **what is happening across** ~~our vision and to receive feedback on matters important to them~~ **the business** ~~. Additionally~~ , ~~we have dynamic~~ **and often include guest speakers, such as Patient Ambassadors, to motivate and inform our employees. Lastly, the Human Resources function recently created an employee self- service portal to allow employees to find useful** information **quickly and easily without assistance** ~~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 (" 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 While we have reported net income in the years ended December 31, **2024,** 2023 and 2022, we cannot assure that we will continue to do so and may not be able to maintain profitability. We have incurred significant **cumulative** operating losses since our inception. While we have reported net income in the years ended December 31 **, 2024** , 2023 and 2022, we cannot assure that we will continue to do so and will need to

continue to generate significant revenue to sustain operations and successfully commercialize neratinib and develop alisertib. As of December 31, ~~2023~~ **2024**, we had an accumulated deficit of approximately $ 1, ~~345~~ **314**. ~~2~~ **9** million, outstanding indebtedness of approximately $ ~~99~~ **67**. ~~7~~ **0** million and cash and cash equivalents and marketable securities of approximately $ ~~95~~ **101**. ~~9~~ **0** million. We expect to continue to incur significant expenses and may incur net losses in the future. Since inception, 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. In September 2022, we in- licensed the development and global commercialization rights to our drug candidate, alisertib. Biopharmaceutical development is a highly speculative undertaking and involves a substantial degree of risk. While we experienced profitability in **2024,** 2023 and 2022, we may incur operating losses in the future as we continue our efforts to commercialize NERLYNX in existing indications and to develop ~~NERLYNX~~ **neratinib** for additional indications, and as we commence development efforts for alisertib and any other drug candidates we may acquire. 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 ago. **We** ~~Although we have begun to commercialize NERLYNX in the United States and Europe in these indications, we continue to experience net losses. Moreover, we~~ are **also** in the early stages of development for alisertib. 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 are only in the preliminary stages of most of these activities, particularly as they relate to alisertib. We will need to generate significant revenue in order to offset our expenses and maintain profitability. We may not be able to generate this revenue or maintain profitability in the future. As a result, we expect to incur losses for the foreseeable future. Accordingly, we cannot assure you that we will be able to maintain or increase profitability. Our failure to maintain profitability could negatively impact the value of our common stock. 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 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. The future 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 any perceived efficacy limitations or related side effects, including diarrhea, or otherwise, the commercial success of NERLYNX will be limited. Thus, significant uncertainty remains regarding the future commercial potential of NERLYNX. We believe our ability to effectively increase product revenue from NERLYNX depends on our ability to, among other things: • achieve and maintain compliance with regulatory requirements; • create and sustain market demand for NERLYNX through our marketing and sales activities and other arrangements established for the promotion of NERLYNX; • compete with other breast cancer drugs, including clinical trials (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; • ensure and maintain appropriate placement on formularies and pathways; • 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; • 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; • maintain broad levels of coverage and reimbursement for NERLYNX from commercial health plans and governmental health programs; • continue to 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; • maintain acceptance of NERLYNX as safe and effective by patients and the medical community; • influence the nature and volume of publicity relative to our competitors' products; • obtain regulatory approvals for additional indications for the use of ~~NERLYNX~~ **neratinib**; 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 ongoing 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 make it difficult to predict our future commercial opportunity and forecast our financial performance. Our operations have consumed substantial amounts of cash since inception. As we continue to commercialize NERLYNX and as we pursue development of alisertib, 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 drug candidates, including conducting clinical trials. Our future capital requirements will depend on many factors, including: • the costs and expenses of our United States 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 developing ~~NERLYNX~~ **neratinib** for additional indications, alisertib and our other drug candidates; • the emergence of competing products; • the extent to which NERLYNX or any other drug candidates we develop are adopted by the physician community and patients; • the number and types of future drug candidates 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 incur 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 and develop alisertib. 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 drug 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 NERLYNX, 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. We are party to a Note Purchase Agreement with Athyrium Opportunities IV Co- Invest 1 LP (“ Athyrium ”), providing for potential issuance by us of notes of up to $ 125. 0 million, which mature on July 23, 2026. 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, ~~2023~~ **2024** , the aggregate principal amount outstanding under the notes sold pursuant to the Note Purchase Agreement (collectively, the “ Athyrium Notes ”) was $ ~~100~~ **66** . ~~0~~ **7** million. The Athyrium Notes are secured by collateral which consists of our equity interests in our domestic and foreign ~~subsidiaries~~ **subsidiary** (including up to 100 % of the issued and outstanding equity interests in ~~each of~~ our ~~domestic subsidiaries~~ **subsidiary** directly owned by us or the guarantors of the Athyrium Notes) and substantially all of our property. In addition to voluntary prepayments, we may also be required to make mandatory prepayments under the Athyrium 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~~ **subsidiary** . 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 (other than certain “ excluded 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 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 Athyrium 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 Athyrium 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 thirty (30) days after its entry and (v) the delisting of our shares of common stock from the Nasdaq Capital Market. Risks Related to the Discovery and Development of our Products and Drug Candidates We have in- licensed alisertib, a drug candidate for which we have assumed all responsibility for global development and commercialization. Our development of alisertib will be expensive, lengthy and unpredictable, and any failure to successfully develop alisertib will have a material adverse effect on our business and financial position. In September 2022, we in- licensed alisertib from Takeda. Pursuant to our exclusive license agreement with Takeda, we are responsible for global development and commercialization of alisertib. Clinical development of alisertib will be expensive, lengthy and unpredictable. Failure or delay can occur at any time during the development process. There are numerous risks associated with our planned development alisertib, including, among others: • We have limited experience developing alisertib; • The results of pre- clinical studies and early clinical studies of alisertib may not be predictive of later clinical studies, and success in previous stages cannot ensure positive outcome of future stages of clinical studies; • Alisertib may fail to show the desired pharmacological properties or safety and efficacy traits despite having progressed through pre- clinical studies and early clinical studies; • Even if we complete clinical development of alisertib, the results may not be sufficient to obtain regulatory approval in the United States or other countries; • Our license agreement with Takeda may be terminated by Takeda if we materially breach the agreement, in which case we would lose all rights to develop and commercialize alisertib; • We plan to rely on third party contractors to formulate and manufacture alisertib for clinical trials and these third- party contractors may be unable to formulate and manufacture alisertib in the volume and quality we require; • We plan to rely on third- party contractors to conduct our clinical trials of alisertib and if those parties fail to perform their services within expected timelines or fail to comply with regulatory requirements, our development efforts could be delayed; • Clinical trials are expensive, time- consuming and difficult to design and implement; and • Development of alisertib could distract management' s attention from other important aspects of our business. Even if we are successful in developing alisertib, we cannot assure you that we will be able to successfully commercialize alisertib. Any delays or failure in our development of alisertib could have material adverse effects on our business, operations and financial condition. 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 drug 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 drug candidates may be harmed, which could harm our business, operating results, prospects or financial condition. NERLYNX, alisertib or 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, alisertib or 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 regulatory authorities. To date, subjects treated with NERLYNX have experienced drug- related side effects such as 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 drug 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 suspend marketing of a product, or we may decide to remove such product from the marketplace; • we may be required to create a medication guide outlining the risks of such side effects for distribution to patients; • we could be subject to fines, injunctions, or the imposition of criminal or civil penalties, or 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 drug candidate, if approved, and could significantly harm our business, results of operations and prospects. We are in the early stages of development of alisertib, and we cannot be certain that we will be successful if we seek regulatory approvals for our drug candidates. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to the development of alisertib. 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 cannot predict with any certainty that any NDA or supplemental NDA (or similar foreign applications) to market alisertib or our other drug candidates will be approved by the FDA or foreign regulatory authorities. We are not permitted to market ~~NERLYNX~~ **neratinib** for other indications or alisertib or any of our other drug candidates in the United States until we receive approval of an NDA from the FDA or until we receive ~~a~~ **an** MA from the EC in the EU, as applicable, for such indications, or, in any foreign countries, until requisite approval from such countries. Approval of ~~NERLYNX~~ **neratinib** by the FDA or the EC for any particular indication does not ensure that another foreign jurisdiction will also approve ~~NERLYNX~~ **neratinib** for such indication, nor does it ensure that ~~NERLYNX~~ **neratinib** will be approved by the FDA or the EC for any other indications. Similarly, approval of alisertib by the FDA or the EC would not ensure that another jurisdiction will also approve alisertib. 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, alisertib or any other drug candidate is safe and effective as a treatment for our targeted indications to the satisfaction of the FDA or other foreign regulator; • the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or other foreign regulator for marketing approval; • the FDA or other foreign 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 foreign regulators may not find the data from pre-clinical studies and clinical trials sufficient to demonstrate that the clinical and other benefits of NERLYNX, alisertib or any other drug candidate outweigh the safety risks; • the FDA or other foreign regulators 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 foreign regulators may not accept data generated at our clinical trial sites; • the FDA or other foreign regulators may require development of a Risk Evaluation and Mitigation Strategy or similar risk management measures as a condition of approval; • the FDA or other foreign regulators may identify deficiencies in the manufacturing processes or facilities of our third- party manufacturers; or • the FDA or other foreign regulators may change their approval policies or adopt new regulations. If we do not obtain regulatory approval of alisertib or our other drug candidates in a particular jurisdiction, we will not be able to market such drug candidate in that jurisdiction. Therefore, failure to obtain regulatory approval of alisertib or our other drug candidates will limit our commercial revenue. In addition, FDA and foreign regulatory authorities may change their approval policies and new regulations may be enacted. For instance, the EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European Commission' s proposal for revision of several legislative instruments related to medicinal products (**potentially reducing the duration of regulatory data protection,** revising the eligibility for expedited pathways, etc.) was published on April 26, 2023. The proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not expected before early 2026. The revisions may however have a significant impact on the biopharmaceutical industry in the long term. We are subject to ongoing obligations and continued regulatory review with regard to NERLYNX, alisertib and any other drug candidates that may receive FDA or foreign regulatory approval, which may result in significant expense. Additionally, NERLYNX, alisertib and our other 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 for NERLYNX and any regulatory approvals that we receive for alisertib or 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 outside the United States. 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, **in recent** ~~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, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points ~~. Even though the FDA resumed standard inspection operations and any resurgence of the virus or emergence of new variants may lead to further inspectional or administrative delays~~ . 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 two limited indications, alisertib 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 ~~have no prior experience developing alisertib and~~ may face significant difficulties during our development of alisertib. 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 for any of our 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 or a positive opinion from one or more institutional review boards (" 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 drug 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 drug 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 drug 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 (" cGMP "), regulations or other applicable requirements, or infections or cross- contaminations of drug 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 (" 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 foreign 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. 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 foreign regulator finds deficiencies in our IND or comparable submissions supporting 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 foreign 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 EU Clinical Trials Directive required a separate CTA to be submitted in each member state in which the clinical trial takes place, 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 for multi- center trials. 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 **ended on** ~~. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to~~ January 31, ~~2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31,~~ 2025 ~~. After this date~~ , **and** all clinical trials (~~including those which~~ **and related applications)** are **now fully** ~~ongoing) will become~~ subject to the provisions of the CTR. Compliance with the CTR requirements by us and our third- party service providers, such as CROs, may impact our developments plans. 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 drug 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 drug 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 drug candidates. Even if regulatory approval is secured for any of our drug candidates, the terms of such approval may limit the scope and use of our drug 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 drug candidates. We may attempt to secure approval from the FDA through the use of the accelerated approval pathway. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary regulatory approvals. Even if we receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post- marketing requirements, the FDA may seek to withdraw any accelerated approval we have obtained. We may in the future seek accelerated approval for our one or more of our drug candidates, including alisertib. Under the accelerated

approval program, the FDA may grant accelerated approval to a drug candidate designed to treat a serious or life- threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the drug candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor' s agreement to conduct, in a diligent manner, additional confirmatory studies to ~~verity~~ **verify** and describe the drug' s clinical benefit. If such post- approval studies fail to confirm the drug' s clinical benefit or are not completed in a timely manner, the FDA may withdraw its approval of the drug on an expedited basis. In addition, in December 2022, **former** President Biden signed an omnibus appropriations bill to fund the U. S. government through fiscal year 2023. Included in the omnibus bill is the Food and Drug Omnibus Reform Act of 2022, which among other things, provided FDA ~~new~~ statutory authority to mitigate potential risks to patients from continued marketing of ineffective drugs previously granted accelerated approval. Under these provisions, the FDA may require a sponsor of a product seeking accelerated approval to have a confirmatory trial underway prior to such approval being granted. Prior to seeking accelerated approval for any of our drug candidates, we intend to seek feedback from the FDA and will otherwise evaluate our ability to seek and receive accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit an NDA **, or NDA supplement,** for accelerated approval or any other form of expedited development, review or approval. Furthermore, if we decide to submit an application for accelerated approval for our drug candidates, there can be no assurance that such application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our drug candidate would result in a longer time period to commercialization of such drug candidate, if any, could increase the cost of development of such drug candidate and could harm our competitive position in the marketplace. Risks Related to Commercialization of our Drug 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 in the commercialization of NERLYNX, our business, results of operations and financial condition may be materially adversely affected. 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; and • unforeseen costs and expenses associated with maintaining an independent sales and marketing organization. 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 our products 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 maintain 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. In the United States, we rely on a direct sales force to market NERLYNX. Additionally, for any future products that we successfully develop, we will need to establish or maintain effective sales and marketing capabilities or enter into agreements with third parties to sell or market those products. There are risks with maintaining and growing our own sales and marketing capabilities, including: • unforeseen costs and expenses associated with creating or maintaining 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, or any additional drug candidates that we develop, could be harmed, which would negatively impact our ability to generate product revenue. Outside the United States we rely entirely on third- party sublicenses for the development and commercialization of NERLYNX. For a description of the risks associated with those arrangements see, " — 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. " NERLYNX was approved by the FDA in 2017. We had total revenue for NERLYNX of $ ~~253~~ **230** . ~~2~~ **5** million, **$ 235. 6 million and** $ 228. 0 ~~million and $ 235. 6~~ million for the years ended December 31, ~~2021~~ **2024** , **2023 and** 2022 ~~and 2023~~ , respectively. We cannot assure you that the sales of NERLYNX will continue at these levels or grow. We may encounter delays or hurdles related to our sales efforts that affect amount of revenue generated and the timing of such revenue. There is no guarantee that the infrastructure, systems, processes, policies, personnel, relationships and materials we have built to commercialize NERLYNX in the United States will be sufficient for us to achieve success at the levels we expect. Our NERLYNX commercialization efforts may fail to gain sufficient market acceptance by physicians, patients, third- party payors and others in the medical community. If NERLYNX does not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not maintain profitability. The degree of market acceptance of NERLYNX and will depend on a number of factors, including: • the timing of our receipt of any additional marketing approvals; • the terms of any approvals and the countries in which approvals are obtained; • the efficacy and safety and potential advantages and disadvantages compared to alternative treatments; • the prevalence and severity of any side effects associated with our products; • the additional indications for which our products are approved; • adverse publicity about our products or favorable publicity about competing products; • the approval of other products for the same indications as our products; • our ability to offer our products for sale at competitive prices; • the convenience and ease of administration compared to alternative treatments; • the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; • the success of our physician education programs; • the strength of our marketing and distribution support; • the availability of third- party coverage and adequate reimbursement, including patient cost- sharing programs such as copays and deductibles; and • any restrictions on the use of our products together with other medications. If NERLYNX fails to achieve market acceptance, it could have a material and adverse effect on our business, financial condition, results of operation and prospects. The majority of our revenue comes from a limited number of customers. In ~~2023~~ **2024** , four customers individually comprised approximately ~~31~~ **28** . 4 %, ~~17~~ **18** . ~~2~~ **8** %, ~~15~~ **14** . ~~2~~ **1** % and ~~11~~ **12** . ~~9~~ **3** % 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. Outside the United States we rely primarily on third- parties to pursue regulatory approval, if necessary, and to commercialize NERLYNX and they may not commit sufficient time or resources to marketing NERLYNX. Outside the United States, we seek to enter into exclusive sub- license agreements with third parties to pursue regulatory approval, if necessary, and commercialize NERLYNX, if approved. As of December 31, ~~2023~~ **2024** , NERLYNX has received approval for the treatment of certain patients with extended adjuvant **and /** or metastatic HER2- positive breast cancer in more than ~~20~~ **40** countries outside the United States, including the EU, Australia, Canada, and Hong Kong. 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, the Middle East and Africa. We depend on these third parties for a significant portion of our total revenue. Royalty revenue obtained pursuant to these sub- license agreements was **15 %,** 14 % and 12 % of total revenue for the years ended December 31 **, 2024** , 2023 and 2022, respectively. We have very little control over these third- parties and any of our existing or future licensees may fail to devote the necessary resources and attention to obtain regulatory approval, where needed, and to market and distribute NERLYNX effectively. If these licensees are unsuccessful in receiving regulatory approvals or in commercializing NERLYNX, our business, results of operations and financial condition will be materially adversely affected. Moreover, we intend to seek additional third parties to sub- license NERLYNX in additional geographies, and may pursue a similar strategy for any future drug candidates that we develop. We cannot assure you that we will be able to enter these agreements on commercial terms, or at all, and our failure to do so would have an adverse effect on our continued commercialization efforts for NERLYNX or any future drug candidates. Even though the FDA and EC have granted approval of NERLYNX for the extended adjuvant treatment of certain patients with early stage, HER2- positive breast cancer and the FDA has granted approval for NERLYNX for the treatment of certain patients with 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 certain adult patients with 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~~ **neratinib** , 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 our products 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 regulate 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 outside the United States may choose, and are generally permitted, to prescribe drugs for uses that are not described in the product' s labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, our ability to promote the products is narrowly limited to those indications that are specifically approved by the FDA 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. **In addition, in December 2024, we announced that NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) for Cervical Cancer were updated to include an addition involving neratinib. The updated NCCN Practice Guidelines for Cervical Cancer include neratinib monotherapy for use as second- line or subsequent therapy for recurrent or metastatic disease as an option for patients with HER2- mutated tumors with a designation of Category 2A. The NCCN Guidelines Category of Preference is designated as " useful in certain circumstances " as a treatment option for patients with HER2- mutated tumors.** Use, as designated for breast cancer patients with brain metastases **and in Cervical Cancer** , 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 outside the United States generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off- label use. Although court decisions in the United States have suggested 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 other 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 other regulatory authorities rules and guidelines relating to promotion and advertising may cause the FDA or other 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. We may fail to obtain orphan drug designations from the FDA for our drug candidates, and even if we obtain such designations, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity. Regulatory authorities in some jurisdictions, including the U. S., may designate drugs designed to address relatively small patient populations as " orphan drugs. " Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200, 000 in the United States, or a patient population greater than 200, 000 in the United States, where there is no reasonable expectation that the cost of developing the drug or biologic will be recovered from sales in the United States. In the U. S., orphan designation entitles a party to financial incentives such as opportunities for grant funding for clinical trial costs, tax advantages and user- fee waivers. In addition, if a drug candidate that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. We may decide to seek Orphan Drug Designations for alisertib. There can be no assurances that we will be able to obtain such designations. Even if we, or any future collaborators, obtain orphan drug designation for a drug candidate, we, or they, may not be able to obtain or maintain orphan drug exclusivity for that drug candidate. Further, even if we, or any future collaborators, obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active ingredients may be approved for the same disease or condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same disease or condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care, or the manufacturer of the product with orphan exclusivity is unable to maintain sufficient product quantity. Orphan drug designation neither shortens the development or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. Health care reform measures may hinder or prevent our products' and drug candidates' commercial success. The United States and some foreign jurisdictions have enacted or are considering enacting a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to profitably sell our product and drug 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 **Affordable Care Act (" ACA ")** became law in the United States. The ACA substantially changed the way healthcare is financed by both governmental and private insurers and significantly affects the pharmaceutical

industry. Among ~~the~~ **other** provisions ~~of ,~~ the ACA **included** ~~, 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~~ **and a new formula that** ~~increase~~ **increases** ~~of~~ the rebates a manufacturer must pay under the Medicaid Drug Rebate Program ~~; • 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 outpatient 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 340B 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. **Thus, the ACA will remain in effect in its current form.** 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, led to reductions to Medicare payments ~~of~~ **to** providers **that** ~~which,~~ will remain in effect through 2032. 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. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminated the statutory Medicaid drug rebate cap, beginning January 1, 2024. The rebate was previously capped at 100 % of a drug' s average manufacturer price, Most significantly, in August 2022, President Biden signed the Inflation Reduction Act of 2022 **(“** ~~, or the~~ IRA ~~,~~**”)** into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare ~~(beginning in 2026)~~ , with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); **redesigns the Medicare Part D benefit (beginning in 2024);** and replaces the Part D coverage gap discount program with a new **manufacturer** ~~discounting~~ --- **discount** program (beginning in 2025). **U. S. Centers for Medicare & Medicaid** ~~The IRA permits the Secretary of the Department of Health and Human~~ Services (~~HHS~~ **“ CMS ”**) ~~to implement many of these provisions through guidance, as~~ **has** ~~opposed to regulation,~~ **published the negotiated prices** for the initial **10 drugs** ~~years. On August 29~~ , **which will first be effective in** ~~2023~~ **2026** , ~~HHS announced~~ **and has published** the list of the ~~first ten~~ **subsequent 15** drugs that will be subject to ~~price negotiations~~ - **negotiation. The IRA permits the Secretary of the Department of Health and Human Services (“ HHS ”) to implement many of these provisions through guidance, as opposed to regulation, for the initial years** . HHS has ~~issued~~ and will continue to issue **and update** guidance **as these programs are** ~~implementing~~ **implemented** ~~the IRA~~ , although the Medicare drug price negotiation program is currently subject to legal challenges. **The** ~~While the~~ impact of the IRA on **us** ~~our business~~ and the pharmaceutical industry cannot yet be fully determined **but** ~~, it~~ is likely to be significant **. NERLYNX is reimbursed under Medicare Part D, and the reimbursement amount will be impacted by the 10 and 20 percent discounts under the IRA' s new discounting program (as noted above). We anticipate that these increased discounts will impact NERLYNX revenues over time, while also having an industry- wide impact on the patient out- of- pocket costs of Part D drugs. The impact on NERLYNX revenues could be offset because the IRA' s redesign of certain Part D components, some of which went into effect in 2024, resulted in an increase in the number of patients able to afford this therapy. The amount of the offset, if any, is inherently uncertain and difficult to predict** . 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. 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 **. Some states have enacted legislation creating so- called prescription drug affordability boards, which ultimately may attempt to impose price limits on certain drugs in these states** . 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 drug candidates, if approved. In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize NERLYNX and our other drug 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 drug candidates, if approved. In other international markets outside the United States and the EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. On December 13, 2021, Regulation No 2021 / 2282 on Health Technology Assessment (“ HTA ”) amending Directive 2011 / 24 / EU, was adopted. **The** ~~While the~~ Regulation entered into force in January 2022 **and has been applicable since** ~~, it will only begin to apply from~~ January 2025 ~~onwards~~ , with ~~preparatory and implementation- related steps to take place in the interim. Once applicable, it will have a~~ phased implementation ~~depending~~ **based** on the ~~concerned~~ **type of product, i. e. oncology and advanced therapy medicinal** products **as of 2025, orphan medicinal products as of 2028, and all other medicinal products by 2030** . This Regulation intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and provide the basis for cooperation at the EU level for joint clinical assessments in these areas. It will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the highest potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non- clinical (e. g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. 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 outside the United States. 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 or any future approved product may lose any regulatory approval that may have been obtained and we may not sustain profitability. Failure to obtain or maintain adequate coverage and reimbursement for our products or drug 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 drug 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 drug 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 drug 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 (" 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. 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 **a revised regulation implementing** 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. 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. Pursuant to the IRA, the AMP figures we report to the MDRP will also be used to compute rebates under Medicare Part D triggered by price increases that outpace inflation. 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. 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 America, South America, the Middle East and Africa. 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. For the years ended December 31, **2024,** 2023 and 2022, royalty revenue from these sub- licensees was $ **35. 3 million, $** 32. 5 million and $ 28. 0 million, respectively, and represented **15 %,** 14 % and 12 % of total revenue, respectively. 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 drug 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 do not intend to establish our own manufacturing facilities. We lack the resources and expertise to formulate or manufacture NERLYNX, alisertib and other potential drug candidates. While our drug candidates were developed by Pfizer and Takeda, both the drug substance and drug product are 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 and we plan to use third- party contractors to manufacture, supply, store and distribute drug supplies for our clinical trials of alisertib. 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 with respect to NERLYNX and any other approved products. 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 or comparable foreign regulatory authority approval. • Our third- party manufacturers might be unable to formulate and manufacture our products and drug candidates 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, alisertib and our other drug candidates must be approved for the manufacture of such products or candidates 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 alisertib and 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 alisertib or our other drug candidates by the FDA or comparable foreign regulatory authorities or the commercialization of NERLYNX ~~,~~ 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 and similar requirements outside the United States, enforced by the FDA through its facilities inspection program and by similar foreign 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, including those involving **neratinib** ~~NERLYNX (for additional indications)~~ and alisertib, 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 cause us to incur additional costs and 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 We and our commercial partners are subject to various risks related to potential future public health emergencies or outbreaks of epidemics, pandemics or contagious diseases, such as the COVID- 19 pandemic. For example, many geographic regions previously imposed, or in the future may impose, " shelter- in- place " orders, quarantines or similar orders or restrictions, which may prevent cancer patients from traveling to see their doctors and result in a decline in new patient enrollments / new patient starts and could adversely affect our business, financial condition and results of operations. Additionally, certain of our personnel, such as our commercial, field medical and sales force teams, were restricted or prevented from conducting routine business activities during the height of the COVID- 19 pandemic, including traveling or interacting in- person with physicians and customers, as a result of these employee health and safety concerns, " shelter- in- place " orders, travel restrictions and other actions and restrictions that may be prudent or required by governmental authorities. Timely enrollment in our clinical trials is dependent upon global clinical trial sites which have been in the past, and may in the future be, adversely affected by the impacts of a potential resurgence of COVID- 19 or other severe global health crises, and disruptions in patient enrollments could have a material adverse impact on our clinical trial plans, timelines, business, financial conditions and results of operations. Additionally, we rely exclusively on third- party manufacturers to manufacture our products. We, our suppliers and our manufacturers modified our business practices for the continued health and safety of our employees during the height of the COVID- 19 pandemic, including by operating with the majority of our respective workforces working from home. If a resurgence of COVID- 19 or other severe global health crisis were to occur, it could disrupt our respective standard operations, including our procurement of suppliers for our operations. 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 public health emergencies or outbreaks of epidemics, pandemics or contagious diseases. 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, if approved, alisertib and our other products; • 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 (" 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 our products. 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 our drug candidates 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. Our internal computer systems and those of third parties with which we contract may be vulnerable to damage from cyberattacks, " phishing " attacks and other social engineering schemes, employee theft or misuse, human error, fraud, denial or degradation of service attacks, computer viruses, malware (e. g. ransomware), sophisticated nation- state and nation- state- supported actors, unauthorized access or use by persons inside our organization or persons with access to systems inside our organization, hacking, 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. 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. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence. 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. The risk of a security breach or disruption, particularly through cyberattacks or cyber intrusion, including by computer hackers, foreign governments and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased and evolved. If we or our third- party vendors were to experience a significant cybersecurity breach of our or their information systems or data, the costs associated with the investigation, remediation and potential notification of the breach to counterparties and data subjects could be material. In addition, our remediation efforts may not be successful. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information. We and certain of our service providers are from time to time subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss, corruption or unauthorized disclosure of our trade secrets, personal information or other proprietary or sensitive information or other similar disruptions. It could also expose us to risks, including an inability to provide our services and fulfill contractual demands, and could cause management distraction and the obligation to devote significant financial and other resources to mitigate such problems, which would increase our future information security costs, including through organizational changes, deploying additional personnel, reinforcing administrative, physical and technical safeguards, further training of employees, changing third- party vendor control practices and engaging third- party subject matter experts and consultants and reduce the demand for our technology and services. If a security breach or other incident were to result in the unauthorized access to or unauthorized use, disclosure, release or other processing of personal information, it may be necessary to notify individuals, governmental authorities, supervisory bodies, the media and other parties pursuant to privacy and security laws. Any security compromise affecting us, our service providers, strategic partners, other contractors, consultants, or our industry, whether real or perceived, could harm our reputation, erode confidence in the effectiveness of our security measures and lead to regulatory scrutiny. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential or proprietary or personal information, we could incur liability, including litigation exposure, penalties and fines, we could become the subject of regulatory action or investigation, our competitive position could be harmed and the further development and commercialization of our products and services could be delayed. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our

business. Furthermore, federal, state and international laws and regulations can expose us to enforcement actions and investigations by regulatory authorities, and potentially result in regulatory penalties, fines and significant legal liability, if our information technology security efforts fail. We may also be exposed to a risk of loss or litigation and potential liability, which could materially and adversely affect our business, results of operations or financial condition. We maintain cyber liability insurance; however, this insurance may not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems. 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 Federal Trade Commission 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. Certain states have also enacted data privacy and security laws and regulations, which govern the privacy, processing and protection of health- related and other personal information. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. For example, the California Consumer Privacy Act of 2018 ~~(" 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 **amended by** ~~well as a private right of action for data breaches that has increased the likelihood of, and risks associated with data breach litigation. Further,~~ the California Privacy Rights Act (**" collectively, the** ~~CPRA~~ **CCPA "** ~~)~~ **requires** ~~generally went into effect on January 1, 2023 and significantly amends the CCPA. It imposes additional data protection obligations on~~ covered businesses **that process the personal information of California residents to, among other things: (i) provide certain disclosures to California residents regarding the business' s collection, use, and disclosure of their personal information; (ii) receive and respond to requests from California residents to access, delete, and correct their personal information, or to opt out of certain disclosures of their personal information; and (iii) enter into specific contractual provisions with service providers that process California residents` personal information on the business' s behalf. Further, Washington State enacted a broadly applicable law to protect the privacy of personal health information known as the " My Health My Data Act, " which generally requires affirmative consent for the collection, use, or sharing of any " consumer health data. " Consumer health data is defined to include personal information that is linked or reasonably linkable to a consumer and that identifies a consumer' s past, present, or future physical or mental health status; consumer health data also includes information that is derived or extrapolated from non- health information, such as algorithms and machine learning. Other states** , including **Connecticut and Nevada, have also passed consumer health data laws, and given the increased focus on the use of health data by entities that are not subject to HIPAA,** additional **states are expected to pass** consumer **health** ~~rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also created a new California data protection agency authorized to issue substantive regulations and could result in increased~~ privacy **laws** ~~and information security enforcement~~ . Additional compliance investment and potential business process changes may also be required. Similar laws have been passed in other states and are continuing to be proposed at the state and 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 also has authority to initiate enforcement actions against entities that mislead customers about HIPAA compliance, make deceptive statements about privacy and data sharing in privacy policies, fail to limit third- party use of personal health information, fail to implement policies to protect personal health information or engage in other unfair practices that harm customers or that may violate Section 5 of the FTC Act. Even when HIPAA does not apply, 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. Additionally, federal and state consumer protection laws are increasingly being applied by the FTC and states' attorneys general to regulate the collection, use, storage, and disclosure of personal or personally identifiable information, through websites or otherwise, and to regulate the presentation of website content. 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 European Union General Data Protection Regulation (" 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 greater. 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, and the efficacy and longevity of current transfer mechanisms between the EEA and the United States remains uncertain. Case law from the Court of Justice of the European Union (" CJEU ") states that reliance on the standard contractual clauses – a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism alone may not necessarily be sufficient in all circumstances and that transfers must be assessed on a case- by- case basis ~~. On October 7, 2022, President Biden signed an Executive Order on ' Enhancing Safeguards for United States Intelligence Activities' which introduced new redress mechanisms and binding safeguards to address the concerns raised by the CJEU in relation to data transfers from the EEA to the United States and which formed the basis of the new EU- US Data Privacy Framework (" DPF "), as released on December 13, 2022.~~ The European Commission adopted its Adequacy Decision in relation to the DPF on July 10, 2023, rendering the DPF effective as a GDPR transfer mechanism to U. S. entities self- certified under the DPF. The DPF also introduced a new redress mechanism for EU citizens which addresses a key concern in the previous CJEU judgments and may mean transfers under standard contractual clauses are less likely to be challenged in future. We currently rely on the EU standard contractual clauses to transfer personal data outside the EEA and the UK, including to the United States, with respect to both intragroup and third- party transfers. We expect the existing legal complexity and uncertainty regarding international personal data transfers to continue. In particular, we expect the DPF Adequacy Decision to be challenged and international transfers to the United States and to other jurisdictions more generally to continue to be subject to enhanced scrutiny by regulators. As a result, we may have to make certain operational changes and we will have to implement revised standard contractual clauses and other relevant documentation for existing data transfers within required time frames. Further, since January 1, 2021, companies **must** ~~have to~~ comply with the GDPR and also the UK data protection regime, which imposes separate but similar obligations to those under the GDPR. 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. On October 12, 2023, the UK Extension to the DPF came into effect (as approved by the UK Government), as a UK GDPR data transfer mechanism to U. S. entities self- certified under the UK Extension to the DPF. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business. 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 alisertib 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 foreign 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, ~~2023~~ **2024**, we had ~~185~~ **172** 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 **, or the threat or imposition of substantial tariffs on imports from various countries, including China, Canada and Mexico** . 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 drug 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 **of funds** , 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 our license agreements with Pfizer and Takeda, respectively. Each of these license agreements may be terminated 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 applicable specified major market countries would constitute a material breach of the applicable license agreement. The applicable license agreement may also be terminated if we become involved in bankruptcy, receivership, insolvency or similar proceedings. In the event either license agreement 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 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 by third parties and could be invalidated or rendered unenforceable. 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 drug candidates or products, could threaten our ability to commercialize any of our current or future drug 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 (" AIA "), enacted in 2011. For example, under the AIA, members of the public may seek to challenge an issued patent by petitioning the U. S. Patent and Trademark Office (" USPTO ") to institute a post grant proceeding, such as a Post Grant Review (" PGR "), or Inter Parties Review (" 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 marketplace 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. Additionally, our products may face generic or biosimilar competition before patent exclusivity expires in various jurisdictions. To date, we have been involved in litigation in the United States against the one ANDA applicant that submitted a Paragraph IV certification directed to our patents (Sandoz), and also in China against parties that filed applications and / or received approval for generic versions of ~~Nerlynx~~ **NERLYNX**. In order to eliminate the burden, expense, distraction and uncertainties of litigation, we entered a settlement and license agreement in 2022 that would permit Sandoz to begin selling a generic version of neratinib in the United States on or around December 8, 2030. 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 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 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 USPTO, to determine priority of invention. If third parties file IPR or PGR 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 unpredictable. 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 two installment payments by us of approximately $ 27. 1 million each, which were paid in January and June 2022. On August 3, 2022, the Court ordered final approval of the parties' settlement and dismissed the case, and the matter is now concluded. 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 AgreementSM 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 when the market price is higher than the exercise price 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 (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 (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 (" 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. **Additionally, valuation allowances needed for deferred tax assets that we estimate are more likely than not to be unusable, based on available evidence at the time the estimate is made. For the year ended December 31, 2024, we released $ 7. 1 million of our valuation allowance related to deferred tax assets, and recorded a valuation allowance of $ 343. 5 million as of December 31, 2024. See Note 12 – Income Taxes in the notes to the financial statements included in this Annual Report for further information. The recording of any future increase in or release of all or any portion of our valuation allowance could have a material impact on our reported results and could cause fluctuations in our quarterly and annual results of operations. Moreover, potential changes in the tax law or in our projections could impact our assessment and valuation allowance estimates, which could have a material adverse effect on our business, financial condition and results of operations.** ITEM 1B. UNRESOLVED STAFF COMMENTS