PORTOLA PHARMACEUTICALS INC
Form 10-K
March 01, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the Fiscal Year Ended December 31, 2018

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
Commission File Number: 001-35935

PORTOLA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

| Delaware | 2834 | 20-0216859 |
|---|---|---|
| (State or other jurisdiction of incorporation or organization) | (Primary Standard Industrial Classification Code Number) | (I.R.S. Employer Identification No.) |

270 E. Grand Avenue

South San Francisco, California 94080

(Address of Principal Executive Offices) (Zip Code)

(650) 246-7000

(Registrant’s Telephone Number, Including Area Code)

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

| Title of Each Class: | Name of Each Exchange on which Registered |
|---|---|
| Common Stock, par value $0.001 per share | The Nasdaq Global Select Market |

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

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

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

| Large accelerated filer | Accelerated filer | Non accelerated filer | Smaller reporting company | Emerging growth company |
|---|---|---|---|---|

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates was approximately $1.4 billion computed by reference to the last sales price of $37.77 as reported by the Nasdaq Global Select Market, as of the last business day of the registrant's most recently completed second fiscal quarter, June 30, 2018. This calculation does not reflect a determination that certain persons are affiliates of the registrant for any other purpose.

As of February 15, 2019, the number of outstanding shares of the registrant's common stock, par value $0.001 per share, was 66,821,167.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference to the definitive proxy statement for the registrant's 2019 Annual Meeting of Stockholders to be filed within 120 days of the registrant's fiscal year ended December 31, 2018.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report, including the sections titled “Business,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases you can identify these statements by forward-looking words, such as “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “could,” “would,” “project,” “plan,” “potential” “goal” or the negative or plural of these words or similar expressions. These forward-looking statements include, but are not limited to, statements concerning the following:

- our estimates and projections for the commercial and clinical development of our products and product candidates, including launch strategies, clinical research and trials and regulatory approval, both in the United States and abroad;
- potential indications for our product candidates;
- our expectations and projections regarding existing capital resources and our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;
- our discussion of perceived and projected competitive advantages of our products and product candidates;
- the projected patient populations targeted by our products and product candidates;
- the projected dollar amounts of market opportunities for our products and product candidates;
- the rate and degree of market acceptance of our approved products;
- our ability to successfully build a hospital-based sales force and commercial infrastructure;
- our ability to obtain and maintain intellectual property protection for our products;
- our ability to successfully establish and successfully maintain appropriate collaborations and derive significant value from those collaborations;
- our financial performance; and
- developments and projections relating to our competitors or our industry.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in “Risk factors.” Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. Moreover, except as required by law, neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to actual results or to changes in our expectations.

You should read this report and the documents that we reference in this report and have filed with the Securities and Exchange Commission as exhibits to this report with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

Note Regarding Use of Brand Names

We refer to our two approved drugs in this report as Andexxa® and Bevyxxa®. If approved outside of the United States, each drug may be marketed under different brand names. In addition, an international nonproprietary name ("INN") has been designated for each drug. Our previous INN for Andexxa in the United States was andexanet alfa; however, in the United States this INN has been replaced with "coagulation factor Xa (recombinant), inactivated-zhzo." For the European Union ("EU") and other parts of the world, andexanet alfa could remain the INN for Andexxa. If approved in the EU, we expect to market andexanet alfa under the brand name Ondexxya™. Our use of Andexxa or Bevyxxa in this document in the context of continued development activities or jurisdictions for which we have not yet received regulatory approval should not be read to imply that we have received regulatory approval for any indication or in any jurisdiction not reflected in our product labels or that we will use such brand names in such jurisdictions.

PART I

ITEM 1. BUSINESS

Overview

Portola Pharmaceuticals, Inc.® (the "Company" or "we" or "our" or "us") is a biopharmaceutical company focused on the development and commercialization of novel therapeutics in the areas of thrombosis, other hematologic diseases and inflammation for patients who currently have limited or no approved treatment options. Our headquarters are located in South San Francisco, California.

Our lead product is Andexxa [coagulation factor Xa (recombinant), inactivated-zhzo], the first and only antidote approved by the U.S. Food and Drug Administration ("FDA") for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Bevyxxa (betrixaban), the first and only oral, once-daily Factor Xa inhibitor approved by the FDA for the prevention of venous thromboembolism ("VTE") in adult patients hospitalized for an acute medical illness, is currently being marketed in a limited manner and we are evaluating potential partnership opportunities for this product. We are advancing cerdulatinib, an investigational oral, dual spleen tyrosine kinase ("Syk") and Janus kinase ("JAK") inhibitor in development to treat hematologic cancers. We also have a number of other molecules in earlier stage and pre-clinical development.

Pipeline

| | Description | Approved or Investigational Indication | Stage | Commercial rights |
|---|---|---|---|---|
| Andexxa | Reversal agent for certain Factor Xa (fXa) inhibitors | Patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding | U.S. Approval<br>Positive CHMP Opinion | Worldwide excluding Japan |
| Bevyxxa | Oral fXa inhibitor | Extended duration VTE prophylaxis in acute medically ill patients in-hospital and post discharge for 35-42 days | U.S. Approval | Worldwide |
| Cerdulatinib | Oral, dual Syk and JAK inhibitor | Relapsed/refractory B- and T-cell malignancies | Phase 2a | Worldwide excluding topical formulation in non-oncology indications |

Our strategy

We are building a global, fully integrated biopharmaceutical company. In 2018, we launched two commercial products in the United States: Andexxa and Bevyxxa. In May 2018, we received FDA approval for Andexxa, which allowed us to launch an Early Supply Program in the United States using limited quantities of drug manufactured under our clinical-scale process. On December 31, 2018, we received approval from the FDA to sell product manufactured using our commercial-scale process, and in January 2019, we commenced a full United States Andexxa launch. On March 1, 2019, the Committee for Medicinal Products for Human Use ("CHMP") communicated a positive opinion for conditional marketing approval of Andexxa in the EU, to be marketed under the brand name Ondexxya. Based on the positive CHMP opinion, we anticipate the European Commission ("EC") decision in the second quarter of 2019, although the CHMP vote is not binding on the EC and there can be no assurances that the EC will provide such decision. In January 2018, we launched our first commercial product, Bevyxxa, in the United States. In March 2018, the CHMP issued a negative opinion, recommending that the EMA reject the marketing application for Bevyxxa in

the EU. We requested a re-examination of the initial opinion and in

July 2018, we received a negative re-examination opinion from the CHMP. The European Commission adopted the CHMP opinion in September 2018. While we continue to evaluate paths for the potential approval of Bevyxxa in the EU, there are currently no applications for Bevyxxa pending before the EU regulatory authorities. Commencing in the second half of 2018, we made the decision to prioritize our resources toward the Andexxa launch and reduced marketing efforts for Bevyxxa.

During 2018 and early 2019 we hired key executive management team members, including the following:

- Scott Garland, President and Chief Executive Officer;
- Ernie Meyer, Executive Vice President and Chief Human Resources Officer;
- Glenn Brame, Executive Vice President and Chief Technical Operations Officer;
- John Moriarty, Executive Vice President, General Counsel and Secretary; and
- Sheldon Koenig, Executive Vice President and Chief Commercial Officer.

Key elements of our strategy are as follows:

- Pursue and prioritize the commercial launch of Andexxa in the United States;
- Strategically scale up our field force and increase engagement with medical, scientific and academic professionals and associations to establish Andexxa as the standard of care for life threatening bleeds;
- Obtain regulatory approval of Andexxa in the EU and pursue a commercial launch through either our own efforts or with the assistance of a marketing partner;
- Pursue additional regulatory approvals for Andexxa, including reversal of additional anticoagulants such as edoxaban and enoxaparin, and reversal of Factor Xa inhibitors for emergency surgery/urgent procedures;
- Establish and improve reimbursement and market access for Andexxa;
- Support our commercial marketing partners Bristol-Meyers Squibb Company (“BMS”) and Pfizer, Inc. (“Pfizer”) to advance development of Andexxa for the Japanese market;
- Continue limited focused commercial efforts for Bevyxxa in the United States while pursuing and evaluating other strategic options for Bevyxxa;
- Advance development of cerdulatinib into registration studies for the treatment of hematologic cancers while considering partnering opportunities for cerdulatinib; and
- Continue to advance our current development pipeline and expand it with multiple preclinical or clinical stage product candidates that align with our scientific expertise and experience.

Approved Products

Andexxa

Andexxa is approved by the FDA as a reversal agent for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexxa was approved under the FDA’s Accelerated Approval pathway based on the change from baseline in anti-Factor Xa activity in healthy volunteers. Continued approval for this indication is contingent upon post-marketing study results to demonstrate an improvement in hemostasis in patients.

We have also submitted a centralized Marketing Authorization Application (“MAA”) for Andexxa under the proposed brand name Ondexxya to the European Union’s European Medicines Agency (“EMA”). On March 1, 2019, the CHMP communicated a positive opinion for Conditional Approval of the MAA. Based on the positive CHMP opinion, we expect an EC decision in the second quarter of 2019, although the CHMP opinion is not binding on the EC and there can be no assurances that the EC will provide such decision. We expect the EC decision for Conditional Approval, if obtained, will include several post-authorization requirements, including specific

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obligations to submit a final clinical study report for the randomized controlled trial of Andexxa (US)/Ondexxya (EU), a final clinical study report for the ANNEXA-4 study, and an obligation to provide some additional pharmacokinetic data.

In the U.S., we initially received approval from the FDA in May 2018 to market product manufactured under our Gen 1 process using the clinical-scale process at the facility that produced material for our clinical trials. We conducted a limited launch in the second half of 2018 through an Early Supply Program ("ESP") intended to reach hospitals with a large number of patients with Factor Xa bleeds and able to start using Andexxa during the ESP period. On December 31, 2018, the FDA approved our Gen 2 manufacturing process, which provides commercial scale volume that we believe is sufficient to support a global launch that can meet worldwide commercial demand for at least the next several years. In early January 2019, we began shipping Gen 2 product and commenced a full-scale commercial launch in the United States. If approved in the EU, we will launch using Gen 2 product.

The worldwide use of Factor Xa inhibitors is rapidly growing because of their efficacy and safety profile compared to warfarin and enoxaparin in preventing and treating thromboembolic conditions such as stroke, pulmonary embolism and VTE. This growth has come with a proportional increase in the incidence of hospital admissions and deaths related to bleeding, the major complication of anticoagulation. In 2017, in the U.S. alone, there were approximately 149,000 hospital admissions attributable to Factor Xa inhibitor-related bleeding. We believe that Andexxa has the potential to act as a universal reversal agent for all direct and indirect Factor Xa inhibitors. We plan to continue clinical development to support global approvals as a reversal agent for other Factor Xa inhibitors. In addition, we plan to continue clinical development to support global approvals for reversal of the anticoagulant effects in Factor Xa inhibitor-treated patients who require emergency surgery/urgent procedures.

Andexxa was granted an Accelerated Approval by the FDA with a requirement for a post-marketing study to verify and describe Andexxa's clinical benefit via an open-label, randomized, controlled trial of Andexxa in acute intracranial hemorrhage in patients receiving oral Factor Xa inhibitors. This trial was initiated in early 2019 and we anticipate that it will include approximately 440 patients and compare outcomes of patients treated with Andexxa to the usual care on a 1:1 randomized scheme. We expect to conduct this study globally over approximately four years.

In August 2018, the U.S. Centers for Medicare & Medicaid Services ("CMS") granted a New Technology Add-on Payment ("NTAP") for Andexxa. Under the NTAP, Medicare will provide an add-on payment for Andexxa of up to approximately $14,000 per qualifying case to participating acute care hospitals. This add-on payment will be incremental to the diagnosis related group reimbursement for qualifying Medicare inpatient cases. The NTAP for Andexxa became effective October 1, 2018, and is expected to remain in effect for a period of two to three years.

In February 2019, we announced full results from ANNEXA-4, our Phase 3b/4 trial of Andexxa in patients experiencing acute major bleeding while taking a Factor Xa inhibitor. Data were presented as a late-breaking oral presentation at the International Stroke Conference 2019 and published simultaneously online by The New England Journal of Medicine ("NEJM"). Full data from 352 patients (249 of which were evaluable for hemostatic efficacy; all 352 were evaluable for safety) showed that Andexxa rapidly and significantly reversed anti-Factor Xa activity when administered as a bolus, and sustained this reversal when followed by a 120-minute infusion. Anti-Factor Xa activity is a measure of the anticoagulant activity of apixaban, rivaroxaban, edoxaban and enoxaparin, the anticoagulants studied in ANNEXA-4. Among all 352 patients, 64 percent (n=227) were treated for intracranial hemorrhage ("ICH") and 26 percent (n=90) were treated for a gastrointestinal bleed. Of those evaluated for efficacy 82 percent (n=204) achieved excellent or good hemostasis (stoppage of bleeding) over the 12-hour period following treatment with Andexxa, as determined by an independent adjudication committee.

Within 30 days of enrollment, thrombotic events occurred in 34 patients (9.7 percent) and death occurred in 49 patients (13.9 percent), consistent with previously presented ANNEXA-4 trial results and with the high background

thrombotic risk of the enrolled patient population. The majority of thrombotic events occurred in patients who delayed or did not re-start anticoagulation therapy with a Factor Xa inhibitor during the follow-up period. Among the 100 patients who re-started oral anticoagulation therapy, no thrombotic events were observed. Two patients experienced an infusion reaction and none developed antibodies to Factor Xa or Factor X or neutralizing antibodies to Andexxa.

We hold worldwide commercial rights to Andexxa with the exception of Japan. In 2016, we entered into collaboration agreements with BMS and Pfizer whereby BMS and Pfizer will seek to obtain Japanese regulatory approval and to commercialize Andexxa in Japan. Under the terms of the agreement we received an upfront payment of $15.0 million and are eligible to receive potential regulatory and sales-based milestone payments of up to $90.0 million, as well as tiered single-digit to double-digit royalties based on net sales in Japan. BMS and Pfizer obtained the rights to develop and commercialize Andexxa in Japan and will be responsible for all development, regulatory and commercialization activities. Under the terms of the agreement, BMS and Pfizer will purchase drug from us at cost for both clinical studies and, upon approval, commercial sales in Japan.

Bevyxxa

Bevyxxa is the first and only anticoagulant approved in the U.S. for hospital and extended duration prophylaxis (35 to 42 days) of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. Bevyxxa was approved by the FDA in June 2017 and we commenced the commercial launch in the U.S. in January 2018.

Acutely ill medical patients are those hospitalized for serious medical conditions, including heart failure, stroke, infection and pulmonary disease. Because of their underlying disorder and immobilization, they are at increased risk of developing deep vein thrombosis (“DVT”) and pulmonary embolism (“PE”) blood clots. In the G7 countries, an estimated 24 million acutely ill medical patients are hospitalized each year and are at risk of VTE, either while in the hospital or following discharge. More than one million VTE events and 150,000 VTE-related deaths occur annually in acutely ill medical patients in the G7 countries, despite the standard use of injectable enoxaparin and other heparins in the hospital. More than half of VTE events occur after patients are discharged from the hospital. No other anticoagulant, including enoxaparin or any of the marketed oral Factor Xa inhibitors, is approved for in-hospital and extended-duration VTE prophylaxis in acutely ill medical patients.

In March 2018, the CHMP issued a negative opinion, recommending that the EMA reject the marketing application for Bevyxxa in the EU. We requested a re-examination of the initial opinion and in July 2018, we received a negative re-examination opinion from the CHMP. The EC adopted the CHMP decision in September 2018. While we continue to evaluate paths for the potential approval of Bevyxxa in the EU, there are currently no applications for Bevyxxa pending before the EU regulatory authorities.

We believe that Bevyxxa has significant commercial potential. We anticipate it will require significant additional effort and more resources than we currently have to drive adoption and market acceptance. Following the approval of Andexxa in May 2018, due to our limited resources, we greatly scaled back our commercial efforts for Bevyxxa in the second half of 2018 in order to focus on the commercial launch of Andexxa. We are re-evaluating our marketing strategy for Bevyxxa and also exploring potential partnership and other strategic options for Bevyxxa.

Product Candidates:

Cerdulatinib

Cerdulatinib is our investigational oral, dual spleen tyrosine kinase (Syk) and janus kinase (“JAK”) inhibitor that uniquely inhibits two key cell signaling pathways implicated in certain hematologic malignancies and autoimmune diseases. There is a rationale for inhibiting both Syk (B-cell receptor pathway) and JAK (cytokine receptors) in B-cell malignancies where both targets have been shown to promote cancer cell growth and survival. In addition, pre-clinical data suggest an important role for Syk and JAK in Peripheral T-Cell Lymphoma (“PTCL”) tumor survival.

There is a significant unmet need for the treatment of patients with relapsed/refractory PTCL. Current approved therapies for relapsed/refractory PTCL are all given via IV infusion and have limited activity with overall response rates of approximately 30%. In addition, most of these responses are partial responses. Based on the unmet need and on the activity to date with cerdulatinib, we have prioritized development in PTCL. Following our End of Phase 2 meeting with the FDA in January 2019, the FDA has requested additional data supporting the proposed dose, which we are in the process of submitting. Pending the outcome of our discussions, we hope to start a registrational

study. In addition, we remain focused on development in CTCL and Follicular Lymphoma and are exploring potential paths to approval in these diseases.

The FDA granted cerdulatinib Orphan Drug Designation for the treatment of PTCL in September 2018. The FDA's Office of Orphan Products Development grants orphan status to support development of medicines for the treatment of rare diseases. Orphan Drug Designation may provide certain benefits, including a seven-year period of market exclusivity if the drug is approved, tax credits for qualified clinical trials and an exemption from FDA market application fees. In December 2018, we presented updated interim data from the ongoing Phase 2a study at the Annual Meeting of the American Society of Hematology. Highlights of this data included the following:

- The objective response rate ("ORR") was 34 percent in the PTCL cohort and 26 percent in the cutaneous T-cell lymphoma ("CTCL") cohort.
- Among the subset of patients in the PTCL cohort with Angioimmunoblastic T-cell Lymphoma ("AITL"), the ORR was 57 percent.
- For the PTCL cohort, eleven of 41 patients (27 percent) achieved a complete response ("CR"), and three patients (7 percent) achieved a partial response ("PR"); in the subgroup of 14 patients with AITL, seven patients (50 percent) achieved a CR and one patient (7 percent) achieved a PR; one patient who achieved a CR went on to transplant; and eight responding patients have remained on drug for three to more than 12 months and five patients have had a duration of response of six months or greater.
- In the CTCL cohort, two patients (7 percent) achieved a CR and five patients (19 percent) achieved a PR; responses have been seen in patients with Mycosis Fungoides and Sezary Syndrome; eleven of 23 patients (48 percent) achieved a ≥ 50 percent reduction in skin lesions, based on the Modified Severity Weighted Assessment Tool ("mSWAT"); and rapid improvements in pruritus, or severe itching – a common and often serious condition associated with CTCL – have been observed, as measured by the Likert scale.

Cerdulatinib has demonstrated tolerability in both PTCL and CTCL. The most common grade 3 or greater adverse events across the PTCL and CTCL cohorts with a frequency > 5 percent were lipase increase (23 percent), amylase increase (18 percent), sepsis/bacteremia (8 percent), and neutropenia, pneumonia/lung infection and diarrhea (7 percent each).

In December 2016, we licensed worldwide rights for the development and commercialization of cerdulatinib in topical applications beyond oncology to Dermavant Sciences GmbH ("Dermavant"). We retain full rights to all non-topical formulations, including oral formulations. Dermavant has presented positive Phase 1 results with topical cerdulatinib in atopic dermatitis patients.

Other Early Stage Programs

We have other early research and development programs including an exclusive in-license agreement with SRX Cardio LLC to explore a novel approach to developing a drug in the field of hypercholesterolemia and a collaboration with Ora for the topical Syk inhibitor PRT2761. PRT2761 was recently evaluated in a Phase 2 study for the treatment of allergic conjunctivitis where it met one of the two primary endpoints for the study. Based on these study results, we and Ora are currently exploring the potential to pursue PRT2761 in dry eye and other ocular inflammatory diseases.

Sales and marketing

We target our U.S. sales and marketing efforts at the approximately 1,500 hospitals and out-patient acute care settings that would account for the large majority of the prescribing base for Andexxa. We market Andexxa in the United States using a hospital-based sales force of approximately 118 sales representatives. This sales force is supported by an experienced sales leadership team of regional sales managers and account managers, and our commercial team

comprised of experienced professionals in marketing, access and reimbursement, managed markets, marketing research, commercial operations, and sales force planning and management. Following approval in the EU, we plan to launch in a limited number of countries and also consider potential collaborations. To achieve

global commercialization, we anticipate using a variety of distribution agreements and commercial partnerships in those territories where we do not establish our own sales force.

Customers

Our products are purchased in the United States primarily by hospital purchasers. These hospitals purchase our products through a network of specialty and wholesale distributors. We do not believe that the loss of one of these distributors would significantly impact the ability to distribute our product as we expect that sales volume would be absorbed by the remaining distributors.

Other Key Licenses and Collaborations

As part of our business strategy, we establish collaborations with other companies, universities and medical research institutions to assist in the clinical development and/or commercialization of certain of our products and product candidates and to provide support for our research programs. We also evaluate opportunities for acquiring products or rights to products and technologies that are complementary to our business from other companies, universities and medical research institutions. For more information regarding certain of these relationships, including their ongoing financial and accounting impact on our business, see Notes 3 and 8, Revenue Recognition and Asset Acquisition and License Agreements of the Notes to Consolidated Financial Statements included in Part II, Item 8 of this Annual Report on Form 10-K.

Andexxa

- BMS and Pfizer

In January 2014, we entered into an agreement with BMS and Pfizer to further study Andexxa as a reversal agent for their jointly-owned, FDA-approved oral Factor Xa inhibitor, apixaban, through Phase 3 studies. We are responsible for the cost of conducting this clinical study. Pursuant to our agreement with BMS and Pfizer, we are obligated to provide research, development and regulatory approval services and participate in the Joint Collaboration Committee.

In February 2016, we entered into a collaboration and license agreement with BMS and Pfizer whereby BMS and Pfizer obtained exclusive rights to develop and commercialize Andexxa in Japan. BMS and Pfizer are responsible for all development, regulatory and commercial activities in Japan and we will reimburse BMS and Pfizer for expenses they incur for research and development activities specific to Factor Xa inhibitors other than apixaban. Pursuant to this agreement, we are obligated to provide certain research and development activities outside of Japan, provide clinical drug supply and related manufacturing services and to participate on various committees in exchange for a non-refundable upfront fee of $15.0 million. We are also eligible to receive, contingent payments totaling up to $20.0 million which may be earned upon achievement of certain regulatory events and up to $70.0 million which may be earned upon achievement of specified annual net sales volumes in Japan. We are also entitled to receive royalties ranging from 5% to 15% on net sales of Andexxa in Japan. As provided in this agreement, we have agreed to provide Andexxa at cost in order to supply clinical and commercial demand in Japan.

- Daiichi Sankyo, Inc. (“Daiichi Sankyo”)

In 2013, we entered into an agreement with Daiichi Sankyo to include subjects dosed with edoxaban, its Factor Xa inhibitor product, in one of our Phase 2 proof-of-concept studies of Andexxa. In July 2014, we entered into a second collaboration agreement with Daiichi Sankyo to perform the necessary development and regulatory activities to support potential U.S. and EU regulatory approval of andexanet alfa as a reversal agent for edoxaban. Under this Phase 3 collaboration agreement we received an upfront payment of $15.0 million. So far, we have received $5 million in milestone payments and are eligible to receive additional development and regulatory milestone payments of up to $2.5 million. In 2016, we amended the 2014 agreement to expedite development activities in exchange for

$15.0 million and a net increase in total

eligible milestones of $8.0 million. We have received $4 million in milestone payments under this amended agreement. This amended collaboration agreement will continue in force until the approval of andexanet alfa as a reversal agent for edoxaban by the FDA and EMA.

In 2016, we entered into a collaboration agreement with Daiichi Sankyo to include edoxoban in the clinical studies necessary for approval of Andexxa in Japan. Under the terms of the agreement, we received an upfront payment of $5.0 million and are eligible to receive up to $10.0 million in additional milestone payments based on Japanese regulatory approval of Andexxa as an antidote for edoxaban.

- We have also entered into collaboration agreements with Bayer Pharma, AG and Janssen Pharmaceuticals, Inc. ("Janssen").

Other Programs

- We have a number of license and collaborations with several partners – Millennium Pharmaceuticals, Inc. ("Millennium"), SRX Cardio, LLC, Ora, and Astellas Pharma Inc. ("Astellas").

Competition

Our industry is highly competitive and subject to rapid and significant technological change. While we believe that our development experience and scientific knowledge provide us with competitive advantages, we may face competition from large pharmaceutical and biotechnology companies, smaller pharmaceutical and biotechnology companies, specialty pharmaceutical companies, generic drug companies, academic institutions, government agencies and research institutions and others.

Many of our competitors may have significantly greater financial, technical and human resources than we have. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop or market products or other novel technologies that are more effective, safer or less costly than any that will be commercialized by us, or obtain regulatory approval for their products more rapidly than we may obtain approval for ours. Our success will be based in part on our ability to identify, develop and manage a portfolio of drugs that are safer, more efficacious and/or more cost-effective than alternative therapies.

Andexxa

Currently there are no therapies approved as antidotes for Factor Xa inhibitors. However, Andexxa competes with the off-label use of treatments designed to enhance coagulation including Fresh Frozen Plasma ("FFP"), 4-factor Prothrombin Complex Concentrates ("PCCs"), recombinant activated Factor VII ("rFVIIa"), Vitamin K, protamine or whole blood. In addition, several companies have conducted clinical research on compounds that are intended to reverse the effects of one or more direct Factor Xa inhibitors and which, if developed, may be competitive with Andexxa.

Bevyxxa

In the market for VTE prophylaxis in acute medically ill patients, Bevyxxa competes primarily with enoxaparin, which is marketed as Lovenox® by Sanofi-Aventis U.S. LLC and as a generic pharmaceutical by several manufacturers, and to a lesser extent with other low molecular weight heparins. In addition, Bevyxxa may face competition in the market for acute medically ill patients from the off-label use of other Factor Xa inhibitors. In addition, Janssen has announced its intention to pursue approval for Xarelto® for prevention of VTE in certain acute medically ill patients following hospital discharge based on the results from its Mariner and Magellan trials.

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Cerdulatinib

In the market for the treatment of Follicular Lymphoma ("FL"), PTCL, CTCL, and cerdulatinib, if approved, will compete with existing therapies, such as rituximab and obinutuzumab which are marketed by Chugai Pharmaceutical Co., F. Hoffmann-LaRoche Ltd. and Genentech, Inc., idelalisib, which is marketed by Gilead, brentuximab, which is marketed by Seattle Genetics, Inc. and Takeda Pharmaceutical Company, Ltd, copanlisib, which is marketed by Bayer AG, duvelisib, which is marketed by Verastem, Inc., romidepsin, which is marketed by Celgene Corporation, pralatrexate and belinostat, which are marketed by Spectrum Pharmaceuticals, Inc., mogamulizumab, which is marketed by Kyowa Hakko Kirin; and potentially other therapies currently in development by a number of different companies.

Intellectual property

Our success will significantly depend upon our ability to obtain and maintain patent and other intellectual property and proprietary protection for our drug candidates, including composition-of-matter, dosage and formulation patents, as well as patent and other intellectual property and proprietary protection for our novel biological discoveries and other important technology inventions and know-how. In addition to patents, we rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain our competitive position. We protect our proprietary information, in part, using confidentiality agreements with our commercial partners, collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention assignment agreements with our commercial partners and selected consultants. Despite these measures, any of our intellectual property and proprietary rights could be challenged, invalidated, circumvented, infringed or misappropriated, or such intellectual property and proprietary rights may not be sufficient to permit us to take advantage of current market trends or otherwise to provide competitive advantages. For more information, please see the section of this Report entitled "Risk factors—Risks related to intellectual property."

Andexanet alfa

Our Factor Xa inhibitor antidote patent portfolio is wholly owned by us and includes 12 issued U.S. patents and ten U.S. patent applications covering the composition of and methods of making and using andexanet alfa or its analogs. We retain full commercialization rights to andexanet alfa on a worldwide basis except for Japan where commercial rights have been licensed to BMS and Pfizer.

The last to expire of the U.S. patents relating to the composition of matter is not expected to expire before June 2030. Related international patent applications have issued in 44 countries, and additional related international patent applications are pending. These international patents and patent applications, if issued, would not be due to expire before September 2028. Several other international patent applications have issued in Europe, Japan, and other countries, and international patent applications are still pending in Europe and a number of other countries.

Betrixaban

Our betrixaban patent portfolio includes 24 issued U.S. patents and eight U.S. patent applications covering the composition of and methods of making and using betrixaban or its analogs, including those owned by us and those licensed from Millennium. The U.S. issued patents relating to the composition of matter of betrixaban are not due to expire before September 2020 and may be extended up to September 2025, if betrixaban receives the patent term extension we have timely petitioned with the U.S. Patent Office, pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. Related international patent applications have issued in 38 countries. These related international patents would not be due to expire before September 2020.

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In the United States, the Hatch-Waxman Act permits a patent term extension of up to five years for one patent related to an approved therapy. We believe that we are eligible for a full five-year patent term extension for one patent relating to betrixaban.

In addition, the Best Pharmaceuticals for Children Act provides that the period of patent exclusivity for a drug may be extended for six months if the owner of the drug conducts studies of the drug in children pursuant to a request from the FDA. We have commenced a pediatric study of bextrixaban in the United States.

Cerdulatinib

Our dual Syk-JAK inhibitor patent portfolio is owned in part by us and licensed in part from Astellas and includes six issued U.S. patents covering the composition of and methods of making and using cerdulatinib or its analogs. The last to expire of the U.S. patents is not expected to expire before July 2029. Related international patent applications have issued in 51 countries and a related patent application is pending in Brazil. These international patents and patent applications, if issued, would not be due to expire before April 2029.

Trademarks

We plan to market all of our products under a trademark or trademarks we select and we will own all rights, title and interest, including goodwill, associated with such trademarks. In the U.S., Andexxa, Annexa, Bevyxxa and Portola Pharmaceuticals, Inc. are our registered trademarks. Trademark registration is pending for Ondexxya in the U.S. and has been registered in the EU. Andexxa and Ondexxya are our registered trademarks in Japan.

Manufacturing

We rely exclusively on contract manufacturing organizations to manufacture our drugs and drug candidates. The manufacture of pharmaceuticals is subject to extensive U.S. and foreign regulations, which impose various procedural and documentation requirements and govern all areas of record keeping, production processes and controls, personnel and quality control. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. We believe that our current agreements and purchase orders with third-party manufacturers provide for sufficient operating capacity to support anticipated commercial and clinical supply needs for the next several years.

Andexxa

Andexxa is a recombinant biologic molecule produced in living cells, a process that is inherently complex and requires specialized knowledge and extensive process optimization and product characterization to transform laboratory scale processes into reproducible commercial manufacturing processes.

Primary commercial manufacturing of Andexxa bulk drug substance is conducted at Lonza AG (“Lonza”). Drug product manufacturing is conducted at Baxter Pharmaceutical Solutions LLC (“Baxter”). We expect that future clinical studies of Andexxa will also be conducted primarily using product manufactured by these third party manufacturing organizations. We continue to sell inventory from our legacy Gen 1 clinical-scale manufacturing process during our transition of our customer base to Gen 2 manufacturing process, but do not expect to enter into any future commercial manufacturing commitments associated with that Gen 1 process or supplier. We also rely on other third-party manufacturers for packaging, testing and shipping.

Bevyxxa

Bevyxxa is manufactured using common chemical engineering and synthetic processes from readily available raw materials. We have relied on Hovione, Limited ("Hovione"), to manufacture active pharmaceutical ingredient ("API") for Bevyxxa at commercial scale. We also rely on Patheon to manufacture drug product to supply Bevyxxa.

See Note 7 in the Notes to Consolidated Financial Statements contained in the section of this report entitled "Financial Statements and Supplementary Data" and refer to the "Off-balance sheet arrangements and contractual

obligations" portion of this report in the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" for a more detailed description of the agreements, obligations and accounting assessments.

Government regulation

Healthcare and reimbursement regulation

Our sales, promotion, medical education and other activities are subject to regulation by numerous regulatory and law enforcement authorities in the United States, including the FDA, the Federal Trade Commission, the Department of Justice, the CMS, other divisions of the Department of Health and Human Services ("HHS") and state and local governments. Our promotional and scientific/educational programs must comply with, among other laws, federal and state price reporting laws, the anti-kickback provisions of the Social Security Act and state counterparts, the Foreign Corrupt Practices Act, federal and state false claims laws including the federal civil False Claims Act, the Veterans Health Care Act and federal and state transparency laws.

The FDA closely regulates the marketing and promotion of drugs, and a company's failure to comply with FDA requirements may result in 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 by us 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.

Depending on the circumstances, failure to meet these applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private "qui tam" actions brought by individual whistleblowers in the name of the government, refusal to allow us to enter into supply contracts, including government contracts, or integrity oversight and reporting obligations.

Sales of pharmaceutical products depend significantly on the availability of third-party coverage and reimbursement. Third-party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. We anticipate third-party payors will provide reimbursement for our products. However, these third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive studies to demonstrate the cost-effectiveness of our products and the product candidates that we develop may not ultimately be considered cost-effective. It is time consuming and expensive for us to seek reimbursement from third-party payors. Reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis.

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost effectiveness of a particular drug candidate to currently available therapies. For example, the EU provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become 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 competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. 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.

For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, "Affordable Care Act"), was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. The Texas U.S. District Court Judge, as well as the Presidential administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision. Additionally, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation 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.

Foreign regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products to the extent we choose to develop or sell any products outside of the United States. The approval process varies from country to country and the time may be longer or shorter than that required to obtain FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Under European Union regulatory systems, marketing authorization applications may be submitted under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes and optional for those that are highly innovative, provides for the grant of a single marketing authorization that is valid for all European Union member states. For drugs without approval in a European Union member state, the decentralized procedure provides for assessment of a marketing application by one member state, known as the reference member state, and review and possible approval of that assessment by one or more other, or concerned, member states. Under this procedure, an applicant submits an application and related materials to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of related materials within 120 days after receipt the application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on grounds of potential serious risk to public health, the disputed points may be referred to the European Commission, whose decision is binding on all member states.

Clinical Development and Marketing Approvals

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products.

The process required by the regulatory authorities before product candidates may be marketed generally involves the following:

- nonclinical laboratory and animal testing of the product including some that must be conducted in accordance with Good Laboratory Practices;

- submission of an investigational new drug application ("IND") which must become effective before human clinical trials may begin;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug candidate for its intended use;
- pre-approval inspection of manufacturing facilities and selected clinical investigators for their compliance with regulatory requirements; and
- Approval of an NDA, for a drug or a BLA, for a biologic prior to commercial marketing for specific indications for use.

The testing and approval process requires substantial time, effort and financial resources. For example, an independent institutional review board for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial commences at that center. Regulatory authorities or an institutional review board or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Some studies also include an Independent Data Monitoring Committee ("IDMC") which receives special access to unblinded data during the clinical trial and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. The IDMC may halt a trial if it feels that the data demonstrate efficacy of the drug and it is no longer ethical to withhold the drug from patients in the control arm of the study. Human clinical trials are typically conducted in three sequential phases that may overlap.

- Phase 1 – Studies are initially conducted to test the product candidate for safety, dosage tolerance, absorption, metabolism, distribution and excretion in healthy volunteers or patients.
- Phase 2 – Studies are conducted with groups of patients with a specified disease or condition to provide enough data to evaluate the preliminary efficacy, optimal dosages and dosing schedule and expanded evidence of safety. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3 – Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety in an expanded patient population at multiple clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product compared to placebo or current standard of care and provide an adequate basis for product labeling. These trials may be done globally to support global registrations.
- The regulatory authorities may require, or companies may pursue, additional clinical trials after a product is approved. These so-called Phase 4 studies may be made a condition to be satisfied after approval. The results of Phase 4 studies can confirm the effectiveness of a product candidate and can provide important safety information gathered in routine medical practice.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with regulatory manufacturing requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must also develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to establish an appropriate shelf life for the product candidate including data demonstrating that the product candidate does not undergo unacceptable deterioration over its shelf life.

Post-approval requirements

Any products manufactured or distributed by us pursuant to regulatory approvals are subject to continuing regulation, including record-keeping requirements and reporting of adverse experiences. Drug and biologic manufacturers and their subcontractors are required to register their establishments with the regulatory authorities and certain state agencies, and are subject to periodic unannounced inspections by the regulatory authorities and certain state agencies

for compliance with regulatory manufacturing requirements, which impose certain procedural and documentation requirements upon us and our third-party contract manufacturers. We cannot be certain that we

or our present or future suppliers will be able to comply with regulatory manufacturing regulations and other regulatory requirements. If our present or future suppliers are not able to comply with these requirements, the regulatory authorities may halt our clinical trials, require us to recall a product from distribution, or withdraw approval of the marketing application.

Andexxa was granted an Accelerated Approval by the FDA with a requirement for a post-marketing study to verify and describe Andexxa's clinical benefit via an open-label, randomized, controlled trial of Andexxa in acute intracranial hemorrhage in patients receiving oral Factor Xa inhibitors. We expect our anticipated approval in the E.U. will also include several post-approval commitments, including an obligation to submit a final clinical study report from the randomized controlled trial of Andexxa and an obligation to provide some additional pharmacokinetic data.

Research and Development

We invested $216.2 million, $203.7 million and $246.9 million in research and development during the years ended December 31, 2018, 2017 and 2016, respectively.

Employees

As of December 31, 2018, we had 324 full-time employees, 115 of whom were engaged in sales and marketing. Our employees are not represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Legal proceedings

We are not currently a party to any material legal proceedings.

Corporate and Available Information

Our principal corporate offices are located at 270 E. Grand Avenue, South San Francisco, California 94080 and our telephone number is (650) 246-7000. We were incorporated in Delaware in September 2003. Our internet address is www.portola.com. We make available on our website, free of charge, our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC. Our SEC reports can be accessed through the Investors section of our internet website. Further, a copy of this Annual Report on Form 10-K is located at the SEC's Public Reference Rooms at 100 F Street, N.E., Washington, D. C. 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements and other information regarding our filings at http://www.sec.gov. The information found on our internet website is not incorporated by reference into this Annual Report on Form 10-K or any other report we file with or furnish to the SEC.

Item 1A. RISK FACTORS.

Investing in our common stock involves a high degree of risk. You should consider carefully the following risks, together with all the other information in this report, including our financial statements and notes thereto, before you invest in our common stock. If any of the following risks actually materializes, our operating results, financial condition and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

In assessing these risks, you should also refer to other information contained in this annual report on Form 10-K, including our Consolidated Financial Statements and related Notes.

1) RISKS RELATED TO OUR FINANCIAL CONDITION AND NEED FOR ADDITIONAL CAPITAL

We have incurred significant losses, and expect to incur substantial and increasing losses as we continue to develop and commercialize our product candidates.

We are an early stage commercial biopharmaceutical company. We launched our first commercial products in 2018 and continue to incur significant expenses related to commercialization, our ongoing and planned future clinical studies, research and development activities, selling, general and administrative activities and charges relating to Bevyxxa. Our operating expenses increased during the year of 2018, and we do not anticipate a significant decrease in the near term. As of December 31, 2018, we had an accumulated deficit of approximately $1.5 billion.

To date, we have financed our operations primarily through sales of our equity securities, collaborations, including a loan from one of our collaboration partners, a sale of a royalty stream from future product sales, sales of commercial and development rights to some of our product candidates, and to a lesser extent, government grants, equipment leases, venture debt and with the benefit of tax credits made available under a federal stimulus program supporting drug development. We have devoted substantially all of our efforts to product commercialization, research and development, including manufacturing and clinical studies. We anticipate that we will continue to incur substantial expenses as we:

- establish and scale-up manufacturing capabilities and a sales, marketing and distribution infrastructure to commercialize our products in the U.S. and abroad;
- initiate or continue clinical studies, including a post-marketing randomized controlled trial of Andexxa;
- continue the research and development of our product candidates;
- seek to discover or in-license additional product candidates;
- seek regulatory approvals for our product candidates that successfully complete clinical studies; and
- enhance operational, compliance, financial, quality and information management systems and hire more personnel, including personnel to support development of our product candidates and support our commercialization efforts.

To be profitable in the future, we must succeed in commercializing our products and developing and commercializing other products with significant market potential. This will require us to be successful in a range of activities, including manufacturing, marketing and selling our products and any other products for which we may obtain regulatory approval, obtaining additional regulatory approvals and successfully completing clinical studies. We are only in the preliminary stages of some of these activities. We may not succeed in these activities and may never generate revenue that is sufficient to be profitable in the future. Even if we are profitable, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to achieve sustained profitability would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our product candidates, market our product candidates, if approved, or continue our operations.

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Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.

Our operating results are difficult to predict and will likely fluctuate from quarter to quarter and year to year. Due to the recent approval by the FDA of our products and the absence of historical sales data, our product sales will be difficult to predict from period to period and as a result, you should not rely on sales results in any period as being indicative of future performance and sales may be below the expectation of securities analysts or investors in the future. We believe that our quarterly and annual results of operations may be affected by a variety of factors, including:

- the level of demand and market acceptance;
- the results of our clinical trials;
- our abilities to obtain desired regulatory approvals in the U.S., EU and other foreign jurisdictions;
- the extent to which coverage and reimbursement is available from government and health administration authorities, private health insurers, managed care programs and other third-party payors;
- rebates, discount, other pricing concessions and fees that we may provide to integrated delivery networks, group purchasing organizations, other purchasers and pharmacy benefits managers and other third-party payors;
- the timing, cost and level of investment in our marketing efforts to support sales;
- the timing, cost and level of investment in our research and development activities involving approved products and product candidates;
- the cost of manufacturing, distribution and the amount of legally mandated discounts to government entities, other discounts and rebates, product returns and other gross-to-net deductions;
- the risk/benefit profile, cost and reimbursement of existing and potential future drugs which compete with approved products;
- the timing and amount of non-cash items such as stock compensation expenses, reserves, cost of goods sold and non-recurring charges such as inventory write-offs; and
- expenditures that we will or may incur to acquire or develop additional product candidates and technologies.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

We will need additional funds to support our operations, and such funding may not be available to us on acceptable terms, or at all, which would force us to delay, reduce or suspend our research and development programs and other operations or commercialization efforts. Raising additional capital may subject us to unfavorable terms, cause dilution to our existing stockholders, restrict our operations, reduce future profitability or require us to relinquish rights to our product candidates and technologies.

We will continue to require substantial funds to support commercial operations and pursue further research and development efforts. Our financing requirements will depend on many factors, some of which are beyond our control, including the following:

- product sales of Andexxa, and if approved for commercial marketing, our product candidates;
- the costs of commercialization activities, including product sales, marketing, manufacturing and distribution and general corporate and commercial infrastructure;
- the costs and timing of international expansion;
- the timing of, and costs involved in, seeking and obtaining approvals from the FDA and other regulatory authorities;
- the possible development of additional product candidates, including through in-licensing and acquisitions;
- the degree and rate of market acceptance of any products launched by us or partners;
- our ability to enter into additional collaboration, licensing, commercialization or other financing arrangements and the terms and timing of such arrangements;
- the rate of progress and cost of our clinical studies; and
- the emergence of competing technologies or other adverse market developments.

Until we can generate a sufficient amount of product revenue to finance our cash requirements, which we may never do, we expect to finance future cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other financing, marketing and distribution arrangements. Additional financing may not be available to us when we need it or it may not be available on favorable terms.

If we raise additional capital through financing, marketing and distribution arrangements or other collaborations, strategic alliances, licensing or other financial arrangements with third parties, we may have to relinquish certain valuable rights to our product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. If we raise additional capital through public or private equity offerings, the ownership interest of our existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and our repayment obligations may reduce future financial performance. If we are unable to obtain adequate financing when needed, we may have to delay, reduce the scope of, or suspend one or more of our clinical studies, research and development programs or commercialization efforts.

Our obligations under our credit facility are secured by substantially all of our assets, so if we default on those obligations, the lenders could foreclose on our assets. As a result of these security interests, such assets would only be available to satisfy claims of our general creditors or to holders of our equity securities if we were to become insolvent at a time when the value of such assets exceeded the amount of our indebtedness and other obligations. Additionally, our credit facility contains restrictions and limitations that could significantly affect our ability to operate our business.

Pursuant to the Credit Agreement by and among us, the guarantor and lenders ("Lenders") party thereto, and HCR Collateral Management, LLC, as Administrative Agent, dated February 28, 2019 (the "Credit Facility"), the Administrative Agent, in its capacity as Collateral Agent for the Lenders, has been granted a security interest in

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substantially all of our assets. As a result, if we default under our obligations to the Lenders, the Collateral Agent could foreclose on its security interest and liquidate some or all of these assets, which would harm our business, financial condition and results of operations.

In the event of a default in connection with our bankruptcy, insolvency, liquidation, or reorganization, the Collateral Agent would have a prior right to substantially all of our assets to the exclusion of our general unsecured creditors. In that event, our assets would first be used to repay in full all indebtedness and other obligations under the Credit Facility, resulting in all or a portion of our assets being unavailable to satisfy the claims of any unsecured indebtedness. Only after satisfying the claims of the Lenders and any unsecured creditors would any amount be available for our equity holders. Events of default under the Credit Facility include, among other things, our failure to pay any amounts due under the Credit Facility or any of the other loan documents, a breach of covenants under the Credit Facility, our insolvency, a material adverse effect occurring, the occurrence of certain defaults under certain other indebtedness for which we are obligated or certain final judgments against us.

The pledge of these assets and other restrictions imposed in the Credit Facility may limit our flexibility in raising capital for other purposes. Because substantially all of our assets are pledged to secure the Credit Facility obligations, our ability to incur additional secured indebtedness or to sell or dispose of assets to raise capital may be impaired, which could have an adverse effect on our financial flexibility.

If we are unable to comply with certain financial and operating restrictions in the Credit Facility, we may be limited in our business activities and access to credit or may default under the Credit Facility.

Provisions in the Credit Facility impose restrictions or require prior approval on our ability, and the ability of certain of our subsidiaries to, among other things:

•Incur additional debt;

•Make certain investments and acquisitions;

•Guarantee the indebtedness of others or our subsidiaries;

•Create liens or encumbrances;

•Engage in new lines of business;

•Enter into transactions with affiliates;

•Pay cash dividends and make distributions;

•Redeem or repurchase capital shares;

•Sell, lease or transfer certain parts of our business or property;

•Prepay other indebtedness; and

•Acquire new companies and merge or consolidate.

The Credit Facility also contains other customary covenants, including covenants that require us to maintain a minimum cash balance of up to $40 million, dependent on borrowings and levels of sales of Andexxa. We may not be

able to comply with these covenants in the future. Our failure to comply with these covenants may result in the declaration of an event of default, which, if not cured or waived, may result in the acceleration of the maturity of indebtedness outstanding under the Credit Facility and would require us to pay all amounts outstanding. If the maturity of our indebtedness is accelerated, we may not have sufficient funds then available for repayment or we may not have the ability to borrow or obtain sufficient funds to replace the accelerated indebtedness on terms

acceptable to us or at all. Our failure to repay our indebtedness would result in the Collateral Agent foreclosing on all or a portion of our assets and possibly force us to curtail or cease our operations.

2) RISKS RELATED TO COMMERCIAL AND MARKETING OPERATIONS AND THE DEVELOPMENT AND COMMERCIALIZATION OF OUR PRODUCTS AND PRODUCT CANDIDATES

Our products may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Our success depends heavily on the launch and commercialization of our products. The commercial success of our products will depend upon their acceptance by the medical community and third-party payors as clinically useful, cost-effective and safe. The degree of market acceptance of any drug depends on a number of factors, such as:

- the prevalence and severity of any side effects;
- efficacy and potential advantages compared to alternative treatments;
- the price we charge for our products;
- interpretations of the results of our clinical trials;
- the willingness of physicians and healthcare organizations to change their current treatment practices;
- the willingness of hospitals and hospital systems to include our products as treatment options;
- 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 willingness of the target patient population to pay for our products, including co-pays under their health coverage plans;
- the strength of marketing and distribution support; and
- the availability of third-party coverage and adequate reimbursement.

Failure to attain market acceptance among the medical community and third-party payors may have an adverse impact on our operations and profitability. If we are not successful in commercializing Andexxa, our future product revenue will suffer, we may incur significant additional losses and our business will be materially harmed.

If we are unable to develop effective sales, marketing and distribution capabilities on our own or through collaborations or other marketing partners, we will not be successful in commercializing our products or our other future products.

We are still in the early stages of developing our sales and marketing infrastructure. To achieve commercial success for our products or any current or potential product candidate, we must continue to develop a sales and marketing organization or outsource these functions to third parties. We plan to market expand our hospital-based sales force in other major markets and work with partners in other parts of the world to commercialize our products globally. There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services.

We also may not be successful entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will 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, which could damage our reputation. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing competing products more successfully than we do.

The development and commercialization of new therapeutic products is highly competitive. We face competition with respect to commercializing our products and developing our current product candidates, and we will face competition with respect to any products that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide.

While there are no therapies other than Andexxa approved specifically as antidotes for Factor Xa inhibitors, we are aware of at least one drug candidate that has been studied in early stage clinical trials as a potential antidote to Factor Xa inhibitors. In addition, Andexxa may compete with the off-label use of other treatments designed to enhance coagulation, such as FFP, PCCs, rFVIIa or whole blood. Although there is no approved indication for these products in patients taking Factor Xa inhibitors, physicians may choose to use them because of familiarity, cost or other reasons. In addition, we are aware that several companies have conducted preclinical research on compounds intended to be antidotes for Factor Xa inhibitors.

For Bevyxxa, several large pharmaceutical and biotechnology companies currently market and sell direct or indirect anticoagulants for use in various disease states, including injectable anticoagulants for the prevention of VTE in acutely ill medical patients. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Some of these competitors are or may be attempting to develop therapeutics for our target indications.

In addition, most of our competitors are large pharmaceutical companies that will have a greater ability to reduce prices for their competing drugs in an effort to gain or maintain market share and undermine the value proposition that we might otherwise be able to offer to payors. Bevyxxa is indicated for the prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors. The current standard of care for VTE prophylaxis in acute medically ill patients in the United States is a 6- to 14-day administration of enoxaparin, marketed as Lovenox and also available in generic form. Enoxaparin is a low cost therapy that is widely accepted by physicians, patients and third-party payors. As a result of this and other factors, we have faced initial difficulties in marketing Bevyxxa in this patient population. Additionally, our competitors may have the financial and other resources to conduct additional clinical studies in an effort to obtain regulatory approval for use of their drugs for VTE prophylaxis in acutely ill medical patients. For example, Bayer and Janssen recently published results from their Phase 3 MARINER clinical trial evaluating the safety and efficacy of rivaroxaban for up to 45 days post hospital discharge (after enoxaparin in hospital) to reduce the risk of symptomatic VTE in medical ill patients. If the results of Bayer and Janssen’s clinical studies support a successful path to regulatory approval, Bevyxxa is expected to face increased competition in the marketplace from a drug that would be used as a different treatment strategy (post discharge only) in an overlapping patient population. Such treatment strategy would not require physicians, patients and third-party payors to replace enoxaparin with a new or higher priced therapy in the hospital.

There are also a number of products in clinical development for hematologic cancer, ophthalmological diseases, allergic rhinitis, allergic asthma and other inflammatory or autoimmune diseases that are potential indications for cerdulatinib or selective Syk inhibitors. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or noncompetitive. Many competing products are in later stages of development than our products and, therefore, may obtain FDA or other regulatory approval for their products before we obtain approval for ours.

Many of our competitors, including a number of large pharmaceutical companies that compete directly with us, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products 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 third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs.

We obtained regulatory approval of Andexxa in the United States through an Accelerated Approval process. Continued approval is contingent upon post-marketing study.

The Accelerated Approval regulations allow drugs that are being developed to treat an unmet medical need to be approved substantially based on evidence of an effect on a biomarker endpoint that is considered reasonably likely to predict clinical benefit rather than a clinical endpoint such as survival or irreversible morbidity. Our approval of Andexxa was supported by data from two Phase 3 ANNEXA studies (ANNEXA-R and ANNEXA-A), which evaluated the safety and efficacy of Andexxa in reversing the anticoagulant activity of the Factor Xa inhibitors rivaroxaban and apixaban in healthy volunteers, and interim patient data from our ongoing ANNEXA-4 single-arm, open-label study in patients on a Factor Xa inhibitor experiencing a life threatening or uncontrolled bleeding episode. However, these studies have inherent limitations as compared with a randomized controlled trial. As a condition to approval, the FDA has required us to conduct a post-marketing randomized controlled trial of Andexxa. This trial will randomize patients to receive either Andexxa or the type of care the enrolling institution would provide in the absence of Andexxa. This study has been opened to enrollment and we expect it to be reported in 2023. We expect the practical implementation and ethical considerations of a randomized controlled trial for Andexxa to present challenges, and we cannot be sure that we will be able to successfully conduct and enroll such a trial in a manner satisfactory to the FDA or within the time period required by the FDA. Further, if the randomized controlled trial is not successful, the FDA could modify or withdraw our marketing approval for Andexxa.

If clinical studies of our product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA or similar regulatory authorities outside the United States or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our future product candidates.

Before obtaining regulatory approval for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of our product candidates in humans. Clinical studies are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A failure of one or more of our clinical studies could occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, clinical studies that could delay or prevent our ability to receive regulatory approval or commercialize our product candidates, including the following:

- the number of patients required for clinical studies of our product candidates may be larger than we anticipate, enrollment in these clinical studies may be insufficient or slower than we anticipate or patients may drop out of these clinical studies at a higher rate than we anticipate;
- clinical studies of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical studies or abandon product development programs;
- the cost of clinical studies or the manufacturing of our product candidates may be greater than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we might have to suspend or terminate clinical studies of our product candidates for various reasons, including unanticipated serious side effects, other unexpected characteristics or unacceptable health risks;
- regulators may not approve our proposed clinical development plans;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical study or conduct a clinical study at a prospective study site;
    - regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements; and
- the supply or quality of our product candidates or other materials necessary to conduct clinical studies of our product candidates may be insufficient or inadequate.

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If we are required to conduct additional clinical studies or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical studies of our product candidates or other testing, if the results of these studies or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications that are not as broad as intended;
- have the product removed from the market after obtaining marketing approval;
- be subject to additional post-marketing testing requirements; or
- be subject to restrictions on how the product is distributed or used.

Our product development costs may also increase if we experience delays in testing or approvals. We do not know whether any anticipated clinical studies will begin as planned, or whether anticipated or ongoing clinical studies will need to be restructured or will be completed on schedule, or at all. Significant clinical study delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which would impair our ability to commercialize our product candidates and harm our business and results of operations.

Failure to obtain regulatory approvals in foreign jurisdictions will prevent us from marketing our products internationally. Following the negative decision by the European Commission, we will not obtain marketing approval to commercialize Bevyxxa in the EU at this time, or potentially ever.

In order to market Andexxa, Bevyxxa or our future products in the European Economic Area ("EEA"), and many other foreign jurisdictions, we must obtain separate regulatory approvals. Specifically, in the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization ("MA"). Before granting the MA, the EMA or the competent authorities of the member states of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

The approval procedures vary among countries and can involve additional clinical testing, and the time required to obtain approval may differ from that required to obtain FDA approval. Clinical studies conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other foreign countries or by the FDA. In addition, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We may not be able to submit for regulatory approvals and even if we submit we may not receive necessary approvals to commercialize our products in any market.

On March 1, 2019, the CHMP communicated a positive opinion for Conditional Approval of our MAA for Andexxa, to be marketed under the brand name Ondexxya in the EU. Based on the positive CHMP opinion, we expect an EC decision in the second quarter of 2019, although the CHMP opinion is not binding on the EC and there can be no assurance that the EC will provide such decision. We expect the EC decision for Conditional Approval, if obtained, will include several post-authorization requirements, including specific obligations to submit a final clinical study report for the randomized controlled trial of Andexxa (U.S.)/Ondexxya (EU), a final clinical study report for the ANNEXA-4 study, and an obligation to provide some additional pharmacokinetic data. The EC may not provide a positive decision and may also delay or further condition such decision. A negative EU outcome or significant delays in EU approval would materially harm our business.

In March 2018, the CHMP issued a negative opinion, recommending that the EMA reject the marketing application for Bevyxxa in the EU. We requested a re-examination of the initial opinion and in July 2018, we received a negative re-examination opinion from the CHMP. The European Commission adopted the CHMP decision in September 2018. Failure to obtain marketing approval of Bevyxxa in the EU will reduce the commercial potential of Bevyxxa and could also have a negative impact on our efforts to commercialize and obtain market acceptance for Bevyxxa in the US market.

If serious adverse side effects are identified with respect to any of our product candidates or either of our approved products, we may need to abandon our development of that product candidate or discontinue sale of that product.

It is impossible to guarantee when or if any of our product candidates will prove safe enough to receive regulatory approval. In addition, there can be no assurance that our clinical studies will identify all relevant safety issues. Known or previously unidentified adverse side effects can adversely affect regulatory approvals or marketing of approved products. In such an event, we might need to abandon marketing efforts or development of that product or product candidate or enter into a partnership to continue development.

While no serious adverse side effects have been observed in our completed healthy subject studies with Andexxa, adverse effects have been observed in our ANNEXA-4 study in bleeding patients. Additionally, there is a risk that adverse events may be reported in our post-marketing randomized controlled trial of Andexxa, additional clinical experience or repeat doses that are determined to have been caused by Andexxa. Some protein-based biologics have encountered problems with immunogenicity, that is, their tendency to trigger an unwanted immune response against themselves. To date, no neutralizing antibodies against Andexxa or antibodies to Factor X or Xa have been detected; however there is still a risk that such antibodies could be identified through our ANNEXA-4 patient study results, additional clinical experience or from repeat doses. In addition, in our ANNEXA-4 patient trial, reversing the anticoagulant activity of Factor Xa inhibitors in patients with life threatening or uncontrolled bleeding who have underlying medical conditions requiring anticoagulation has been associated with thromboembolic events, ischemic events, cardiac arrest and sudden deaths, and the FDA has included a boxed warning in the Andexxa label to this effect.

Bevyxxa, like all currently marketed inhibitors of Factor Xa, carries some risk of life-threatening bleeding. In addition, patients taking Bevyxxa in our Phase 2 studies had an increased rate of gastrointestinal issues, such as diarrhea, nausea and vomiting, and other side effects such as back pain, dizziness, headaches, rashes and insomnia as compared to subjects taking a placebo or an active comparator.

If a regulatory agency discovers adverse events of unanticipated severity or frequency it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. Among other legal and administrative actions, a regulatory agency may:

- mandate modifications to product labelling or promotional materials or require us to provide corrective information to healthcare practitioners;
- suspend any regulatory approvals;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications filed by us, our partners or our potential future partners;
- impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products or require a product recall.

In addition, the occurrence of any of the foregoing, even if promptly remedied, could negatively impact the perception of us or the relevant product among the medical community, patients or third-party payors.

The FDA’s approval of Andexxa was limited to patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, and additional clinical studies and regulatory applications will be required to expand Andexxa indications. We can provide no assurances that such clinical studies or regulatory applications will be successful.

We are developing Andexxa as a universal antidote for patients receiving a Factor Xa inhibitor when reversal of anticoagulation is needed, such as in life-threatening or uncontrolled bleeding or for emergency surgery/urgent

procedures. Our approval of Andexxa was limited to patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Our studies have not yet included patients requiring emergency surgery or urgent procedures and we do not anticipate obtaining this indication without clinical data. We expect that we will also be required to provide additional clinical data to support addition to our label of other Factor Xa inhibitors, including Bevyxxa, edoxaban and enoxaparin. Additional clinical studies will

require additional time and expense and may not prove successful. Limitations in our label for Andexxa will reduce the number of patients for whom Andexxa is indicated and could reduce the size of the anticipated market and our financial prospects. In addition, our label for Andexxa includes a boxed warning that treatment with Andexxa has been associated with serious and life threatening adverse events, thromboembolic events, ischemic events, cardiac arrest and sudden deaths. This boxed warning may adversely impact market acceptance and the commercial potential of Andexxa. There can be no assurance that further clinical experience will provide a basis to remove this boxed warning.

3) RISKS RELATED TO OUR RELIANCE ON THIRD PARTIES

We rely on single source third-party contract manufacturing organizations to manufacture and supply Andexxa, Bevyxxa and our product candidates for us. If one of our suppliers or manufacturers fails to perform adequately or fulfill our needs, we may be required to incur significant costs and devote significant efforts to find new suppliers or manufacturers. We may also face significant delays in the development and commercialization of our product candidates.

We do not own facilities for clinical-scale or commercial manufacturing of our product candidates and we rely on third-party suppliers to manufacture Andexxa, Bevyxxa and our product candidates. For example, we have contracted with Lonza to manufacture Andexxa bulk drug substance and Baxter to manufacture drug product to support our commercial launch. We rely on Hovione to manufacture the active pharmaceutical ingredient for Bevyxxa and Patheon Inc. (part of Thermo Fisher Scientific) to manufacture drug product to supply Bevyxxa. We also rely or expect to rely on other third party providers for raw materials, packaging, labeling and supply chain warehousing and distribution. If we and our suppliers cannot agree to the terms and conditions for them to provide the drug supply necessary for our clinical and commercial needs, or if any single source supplier breaches an agreement with us, or terminates the agreement in response to an alleged breach by us or otherwise becomes unable to fulfill its supply obligations, we would not be able to manufacture and distribute the product candidate until a qualified alternative supplier is identified, which could also significantly disrupt, delay the development of, and impair our ability to commercialize, our product candidates. In addition, lead times for our manufacturing and contractual requirements of our third-party manufacturers require us to estimate product demand in advance. If our forecasts are not accurate, we may experience shortfalls or surplus of product. If we do not manufacture enough product, we may experience stock-outs and interruption of supply of our products. If we manufacture a surplus of product, we may experience spoilage from product expiration and incur manufacturing expenses which were not required. We have fixed manufacturing commitments with our third-party manufacturers which are on a “take-or-pay” basis which could require us to pay for manufacturing costs even if we eventually do not need the capacity forecasted at the time we entered into such commitments. The financial impact of either stock-outs or a product surplus could be significant with respect to financial commitments and the effect on our financial performance.

The manufacture of pharmaceutical products in compliance U.S. and foreign regulatory manufacturing requirements, requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, including difficulties with production costs and yields, quality assurance, including stability of the product candidate and quality control testing, shortages of qualified personnel, as well as compliance with strictly enforced regulatory requirements, other federal and state regulatory requirements and foreign regulations. If our manufacturers were to encounter any of these difficulties or otherwise fail to comply with their obligations to us or under applicable regulations and agreements, our ability to provide the drug supply necessary for our clinical studies and commercial needs would be jeopardized. Any delay or interruption in the supply of clinical study materials could delay the completion of our clinical studies, increase the costs associated with maintaining our clinical study programs and, depending upon the period of delay, require us to commence new studies at significant additional expense or terminate the studies completely.

All manufacturers of our product candidates must comply with regulatory manufacturing requirements enforced by the U.S. and foreign regulatory authorities through their facilities inspection programs. These requirements include, among other things, quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with these manufacturing requirements and with other FDA, state and foreign regulatory requirements. The FDA or similar foreign regulatory agencies may also

implement new standards at any time, or change their interpretation and enforcement of existing standards for manufacturing, packaging or testing of products. We have limited control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall or withdrawal of product approval. If the safety of any product supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products and we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay or interruption of clinical studies, regulatory submissions, approvals or commercialization of our product candidates, entail higher costs or adversely affect our reputation.

Although alternative sources of supply exist, the number of third-party suppliers with the necessary manufacturing and regulatory expertise and facilities to manufacture biologics is limited, and it could be expensive and take a significant amount of time to arrange for alternative suppliers, which could have a material adverse effect on our business. New suppliers of any product candidate would be required to qualify under applicable regulatory requirements and would need to have sufficient rights under applicable intellectual property laws to the method of manufacturing the product candidate. Obtaining the necessary regulatory approvals or other qualifications under applicable regulatory requirements and ensuring non-infringement of third-party intellectual property rights could result in a significant interruption of supply and could require the new manufacturer to bear significant additional costs which may be passed on to us.

We rely on third parties to conduct our clinical studies, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such studies.

We do not independently conduct clinical studies of our product candidates. We rely on third parties, such as contract research organizations ("CROs"), clinical data management organizations, medical institutions and clinical investigators, to perform this function. Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. We remain responsible for ensuring that each of our clinical studies is conducted in accordance with the general investigational plan and protocols for the study.

Moreover, the regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting the results of clinical studies to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of patients in clinical studies are protected. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical studies in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully develop our products and our product candidates.

We also rely on other third parties to store and distribute supplies for our clinical studies. Any performance failure on the part of our existing or future distributors could delay clinical development or regulatory approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We may enter into collaborations that place the development and commercialization of our products and product candidates outside our control, require us to relinquish important rights or may otherwise be on terms unfavorable to us, and if our collaborations are not successful, our product candidates may not reach their full market potential.

We may enter into additional collaboration agreements with third parties with respect to our product candidates for the commercialization of the candidates both inside and outside the United States, or for other purposes. For example, we have out-licensed development and commercial rights to Andexxa in Japan. In addition, depending on our capital requirements, development and commercialization costs, need for additional therapeutic expertise and other factors, it is possible that we will enter into broader development and commercialization arrangements with respect to our product candidates. Our likely collaborators for any distribution, marketing, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We will have limited control over the amount and timing

of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend in part on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates are subject to numerous risks, which may include the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to any such collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical study results, changes in their strategic focus due to the acquisition of competitive products, availability of funding or other external factors, such as a business combination that diverts resources or creates competing priorities;
- collaborators may delay clinical studies, provide insufficient funding for a clinical study program, stop a clinical study, abandon a product candidate, repeat or conduct new clinical studies or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to their marketing and distribution;
- collaborators may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- disputes may arise between us and a collaborator that causes the delay or termination of the research, development or commercialization of our product candidates or that results in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates; and
- collaborators may own or co-own intellectual property covering our products that results from our collaborating with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property.

Any termination or disruption of our collaboration with potential collaborators could result in delays in the development and commercialization of our product candidates, increases in our costs to develop and commercialize the product candidate, or the termination of development of a product candidate.

4) RISKS RELATED TO THE OPERATION OF OUR BUSINESS

Our future success depends on our ability to retain our key executives, and if we are not able to retain these members of our management, or retain or recruit additional management and other key personnel, our business will suffer.

Recruiting and retaining leadership and other key personnel is critical to our success. Our former Chief Executive Officer, William Lis, retired in 2018 and our board of directors appointed Scott Garland to serve as our President and Chief Executive Officer. We are highly dependent on Mr. Garland and the other principal members of our executive and leadership teams. We may not be able to attract and retain management and other key personnel in the future, due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the San Francisco Bay Area. We also may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of personnel from universities, research institutions

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and technology companies. In addition, we rely on consultants and advisors to assist us in formulating our business strategies. Our consultants and advisors may also perform services for companies other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Under the terms of their employment, our executives may terminate their employment with us at any time. The loss of the services of any of these people could impede the achievement of our research, development and commercialization objectives.

We expect to expand our development, regulatory and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

Over the next several years, we may experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, quality, commercial compliance, medical affairs, and sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

We incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to existing and new public company compliance and reporting regulations.

As a public company, we incur significant legal, accounting and other expenses. For example, the Sarbanes-Oxley Act, and rules of the Securities and Exchange Commission (“SEC”) and those of The Nasdaq Stock Market, or the Nasdaq, have imposed various requirements on public companies including requiring establishment and maintenance of effective disclosure and financial controls. Our management and other personnel have and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations are continuously being revised, have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. In addition, we are required to have our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting. Our compliance with Section 404 of the Sarbanes-Oxley Act, as applicable, requires us to incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we will need to continue to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. If we or our independent registered public accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources.

Our ability to successfully implement our business plan and comply with Section 404 of the Sarbanes-Oxley Act, as applicable, requires us to be able to prepare timely and accurate financial statements. We expect that we will need to continue to improve existing, and implement new operational and financial systems, procedures and controls to manage our business effectively. Any delay in the implementation of, or disruption in the transition to, new or enhanced systems, procedures or controls, may cause our operations to suffer and we may be unable to conclude that our internal control over financial reporting is effective and to obtain an unqualified report on internal controls from our auditors as required under Section 404 of the Sarbanes-Oxley Act. If we fail to maintain an effective system of

internal control over financial reporting, we may not be able to accurately report our financial results, and current and potential stockholders may lose confidence in our financial reporting. This, in turn, could have an adverse impact on trading prices for our common stock, and could adversely affect our ability to access the capital markets.

Product liability lawsuits and claims against us could cause us to incur substantial liabilities and could limit product sales.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical studies, and the commercial manufacturing, distribution and sale of Andexxa and Bevyxxa. For example, the manufacturers of currently marketed Factor Xa inhibitors and other manufacturers of anticoagulants have faced substantial litigation due to certain alleged bleeding risks. In addition, in our ANNEXA-4 patient trial, reversing the anticoagulant activity of Factor Xa inhibitors in patients with underlying medical conditions requiring anticoagulation has been associated with thromboembolic events, ischemic events, cardiac arrest and sudden deaths, and the FDA has included a boxed warning in the Andexxa label to this effect. If we cannot successfully defend ourselves against claims that Andexxa, Bevyxxa or our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our products;
- injury to our reputation and significant negative media attention;
- withdrawal of patients from clinical studies or cancellation of studies;
- significant costs to defend the related litigation;
- substantial monetary awards to patients;
- loss of revenue; and
- the inability to commercialize any additional products that we may develop.

We may not have sufficient insurance coverage for future product liability claims. We may not be able to obtain insurance in amounts or scope sufficient to provide us with adequate coverage against all potential liabilities. Any product liability claims brought against us, with or without merit, could increase our product liability insurance rates or prevent us from securing continuing coverage, harm our reputation in the industry, significantly increase our expenses, and reduce product sales. Product liability claims in excess of our insurance coverage would be paid out of cash reserves, harming our financial condition and operating results.

We may expend our limited resources to pursue a particular product, product candidate or indication and fail to capitalize on products, product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on sales, marketing and research programs and products and product candidates for specific indications. As a result, we may forego or delay pursuit of opportunities with other products or product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products.

If we do not accurately evaluate the commercial potential or target market for a particular product or product candidate, we may relinquish valuable rights through collaboration, licensing, or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our

operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological or hazardous materials. In addition, we may be required to incur substantial costs to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. Our corporate headquarters is located in California near major earthquake faults. Our operations and financial condition could suffer in the event of a major earthquake, fire or other natural or manmade disaster.

If we obtain approval to commercialize any approved products outside of the United States, a variety of risks associated with international operations could materially adversely affect our business. If any product candidates that we may develop are approved for commercialization outside the United States, we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- differing payor reimbursement regimes, governmental payors or patient self-pay systems and price control;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

In connection with our Andexxa and Bevyxxa development, we are currently utilizing certain suppliers outside of the United States, which subjects us to certain of the above risks.

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We may be subject to information technology system failures, network disruptions and breaches in data security.

We are increasingly dependent upon information technology systems and infrastructure to conduct critical operations and generally operate our business, which includes using information technology systems to process, transmit and store electronic information in our day-to-day operations, including customer, employee and company data. The size and complexity of our computer systems make them potentially vulnerable to breakdown, malicious intrusion and random attack. We also store certain information with third parties. Our information systems and those of our third-party vendors are subjected to computer viruses or other malicious codes, unauthorized access attempts, and cyber- or phishing-attacks and also are vulnerable to an increasing threat of continually evolving cybersecurity risks and external hazards. Disruption, degradation, or manipulation of these systems and infrastructure through intentional or accidental means could impact key business processes. Cyber-attacks against the Company's systems and infrastructure could result in exposure of confidential information, the modification of critical data, and/or the failure of critical operations. Likewise, improper or inadvertent employee behavior, including data privacy breaches by employees and others with permitted access to our systems, may pose a risk that sensitive data may be exposed to unauthorized persons or to the public. Any such breach could compromise our networks, and the information stored therein could be accessed, publicly disclosed, lost or stolen. Such attacks could result in our intellectual property and other confidential information being lost or stolen, disruption of our operations, and other negative consequences, such as increased costs for security measures or remediation costs, and diversion of management attention. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical study data from completed or ongoing clinical studies for any of our product candidates 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 was 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 the further development of our product candidates could be delayed. In addition, with planned operations in EU, we will need to comply with the General Data Protection Regulation ("GDPR") provisions relating to personal data, use of third party processors, data breach notifications and transfer of personal data out of the EU to the United States. The GDPR imposes large penalties for noncompliance and has the potential to increase our responsibility and liability in relation of personal data that we process, including in clinical trials, and we are required to put in place and maintain additional mechanisms to ensure compliance with the GDPR, including increased company and vendor technology and data management measures and cybersecurity investments.

5) RISKS RELATED TO INTELLECTUAL PROPERTY

If we fail to comply with our obligations in our intellectual property licenses from third parties, we could lose license rights that are important to our business.

We are a party to intellectual property license agreements with third parties, including with respect to Bevyxxa, cerdulatinib, and other early stage programs, and we expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that our future license agreements will impose, various supply, support, diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, our licensors may have the right to terminate these agreements or pursue other remedies, in which event we may not be able to develop and market any product that is covered by these agreements or be liable for damages. Termination of licenses or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms or our not having sufficient intellectual property rights to operate our business. The occurrence of such events could materially harm our business.

Our ability to successfully commercialize our technology and products may be materially adversely affected if we are unable to obtain and maintain effective intellectual property rights for our technologies and product candidates.

Our success depends in large part on our and our licensors' ability to obtain and maintain patent and other intellectual property protection in the United States and in other countries with respect to our proprietary technology and products. In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or products that we license from third parties. Therefore, we cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. In addition, if our current or future licensors, licensees, or

collaboration partners fail to establish or maintain such patents and other intellectual property rights, or lose rights to those patents and other intellectual property rights, such rights may be reduced or eliminated.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technologies or from developing competing products and technologies.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unresolved. In recent years patent rights have been the subject of significant litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our and our licensors' patent rights are highly uncertain. Our and our licensors' pending and future patent applications may not result in patents being issued that protect our technology or products or that effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned and licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

The Leahy-Smith America Invents Act, or the America Invents Act ("AIA") implemented significant changes to United States patent law. The AIA could increase the uncertainties and costs surrounding the prosecution of our owned or in-licensed patent applications and the enforcement or defense of our owned or in-licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

We have been and may again become involved in opposition, derivation, reexamination, inter partes review, post-grant review, or other proceedings challenging our patent rights or the patent rights of our licensors, and the outcome of any proceedings are highly uncertain. For example, in November 2013, Zentiva k.s. and Günter SÖLCH separately filed papers with the European Patent Office opposing European Patent 2101760, assigned to Millennium to which we have an exclusive license. The European Patent Office decided in favor of revoking the European patent. Portola has appealed this revocation. Should any of these proceedings or appeals be unsuccessful, this could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner, or by successfully seeking to narrow or invalidate our patents or render them unenforceable. The issuance of a patent is not conclusive as to its inventorship scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us, and may result in loss of exclusivity or

freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop or prevent us from stopping others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a

result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours or otherwise provide us with a competitive advantage.

If we do not obtain patent term extension and data exclusivity for any product candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our owned or licensed U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. Similar extensions as compensation for patent term lost during regulatory review processes are also available in certain foreign countries and territories, such as in Europe under a Supplementary Patent Certificate. However, we may not be granted an extension in the United States and/or foreign countries and territories because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. For example, we have applied for patent term extensions at the U.S. Patent and Trademark Office (USPTO) within the applicable deadline after receiving approval for Andexxa and Bevyxxa, but have not yet received a final determination. If we are unable to obtain patent term extension or the term of any such extension is shorter than what we request or we fail to choose the most optimal patents to extend, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and prospects could be materially harmed.

We may become involved in lawsuits to protect or enforce our patents, which could be expensive, time-consuming and unsuccessful.

Competitors or other parties may infringe our patents. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our products and product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the proprietary rights or intellectual property of third parties. We may become party to, or be threatened with, future adversarial proceedings or litigation regarding third party intellectual property rights with respect to our products, product candidates, and technology, including interference proceedings before the USPTO. An interference proceeding is a proceeding before the USPTO to determine the priority among multiple patents or patent applications. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Any litigation involving defense against claims of infringement, misappropriation or other violation of proprietary or intellectual property rights, regardless of the merit of such claims, would involve substantial litigation expense and would be a substantial diversion of management time. If we are found to infringe a third-party’s intellectual property rights, we could be required to pay substantial damages, including

treble damages and attorneys' fees if we are found to be willfully infringing a third party's patents. We may also be required to indemnify parties with whom we have contractual relationships against such claims. If a patent infringement suit were brought against us, we could be forced to stop or delay research, development, manufacturing or sales of the product or product candidate that is the subject of the suit. We also could be required to obtain a license from such third-party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all.

Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. A finding of infringement could prevent us from commercializing our products or

product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties can have a similar negative impact on our business.

We may be unable to protect the confidentiality of our trade secrets, thus harming our business and competitive position.

In addition to our patented technology and products, we rely upon trade secrets, including unpatented know-how, technology and other proprietary information to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. We also have agreements with our employees and consultants that obligate them to assign their inventions to us. However, it is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees, consultants or collaborators that are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could be disclosed, misappropriated or otherwise become known or be independently discovered by our competitors. In addition, intellectual property laws in foreign countries may not protect our intellectual property to the same extent as the laws of the United States. If our trade secrets are disclosed or misappropriated, it would harm our ability to protect our rights and have a material adverse effect on our business.

We may be subject to claims that our employees have wrongfully used or disclosed intellectual property of their former employers. Intellectual property litigation or proceedings could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee’s former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other intellectual property-related proceedings could have a material adverse effect on our ability to compete in the marketplace.

6) RISKS RELATED TO GOVERNMENT REGULATION

The regulatory approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing and distribution of drug products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other

countries, which regulations differ from country to country. We will not be permitted to market our product candidates in the United States until we receive approval of an NDA or a BLA, from the FDA. Obtaining approval of an NDA or BLA can be a lengthy, expensive and uncertain process that may not be successful. In addition, failure to comply with FDA and other applicable U.S. and foreign regulatory requirements may subject us to administrative or judicially imposed sanctions, including the following:

- warning letters;
- civil or criminal penalties and fines;
- injunctions;

- suspension or withdrawal of regulatory approval;
- suspension of any ongoing clinical studies;
- voluntary or mandatory product recalls and publicity requirements;
- refusal to accept or approve applications for marketing approval of new drugs or biologics or supplements to approved applications submitted by us;
- restrictions on operations, including costly new manufacturing requirements; or
- seizure or detention of our products or import bans.

Prior to receiving approval to commercialize any of our product candidates in the United States or abroad, we must demonstrate with substantial evidence from well-controlled clinical studies, and to the satisfaction of the FDA and other regulatory authorities abroad, that such product candidates are safe and effective for their intended uses. Results from preclinical studies and clinical studies can be interpreted in different ways. Even if we and our collaboration partners believe the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. Administering any of our product candidates to humans may produce undesirable side effects, which could interrupt, delay or cause suspension of clinical studies of our product candidates and result in the FDA or other regulatory authorities denying approval of our product candidates for any or all targeted indications.

Regulatory approval of an NDA or BLA is not guaranteed, and the approval process is expensive and may take several years. The regulatory authorities also have substantial discretion in the approval process. Despite the time and expense exerted, failure can occur at any stage, and we could encounter problems that cause us to abandon or repeat clinical studies, or perform additional preclinical studies and clinical studies. The number of preclinical studies and clinical studies that will be required for FDA approval varies depending on the product candidate, the disease or condition that the product candidate is designed to address and the regulations applicable to any particular product candidate. The FDA can delay, limit or deny approval of a product candidate for many reasons, including, but not limited to, the following:

- a product candidate may not be deemed safe or effective;
- FDA officials may not find the data from preclinical studies and clinical studies sufficient;
- the FDA may find our manufacturing data insufficient to support approval
- the FDA might not approve our or our third-party manufacturer's processes or facilities; or
- the FDA may change its approval policies or adopt new regulations.

If any of our product candidates fails to demonstrate safety and efficacy in clinical studies or does not gain regulatory approval, our business and results of operations will be materially and adversely harmed.

Unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives could harm our business.

There is increasing pressure on biotechnology companies to reduce healthcare costs. In the U.S., these pressures come from a variety of sources, such as managed care groups, institutional, and government purchasers. Increased purchasing power of entities that negotiate on behalf of federal healthcare programs and private sector beneficiaries could increase pricing pressures in the future. Such pressures may also increase the risk of litigation or investigation by the government regarding pricing calculations. The biotechnology industry will likely face greater regulation and political and legal action in the future.

The regulations that govern marketing approvals, pricing and reimbursement for new therapeutic products vary widely from country to country. Some countries, including many EU member countries, require approval of the sale price of a product before it can be marketed. In many countries, including EU member countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. In

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some foreign markets, including the EU member countries, current standard of care and/or competitive products may be used as a benchmark or reference to determine pricing and reimbursement level for novel products such as Andexxa and Bevyxxa. To the extent that comparators are available at lower prices than our anticipated pricing for Andexxa or Bevyxxa, the pricing and reimbursement level of our products in the EU could be negatively impacted. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenue we are able to generate from the sale of the product in that country, or even reduce the commercial viability of the product to an extent that prevents the launch altogether.

Adverse pricing limitations may hinder our ability to recoup our investment in Andexxa, Bevyxxa or one or more product candidates, even if our product candidates obtain regulatory approval. Adverse pricing limitations prior to approval will also adversely affect us by reducing our commercial potential. Our ability to commercialize any products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments becomes available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will cover and establish reimbursement levels.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and these 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 companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We are engaged in ongoing negotiations with hospitals and third-party payors regarding coverage, reimbursement and formulary placement. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Reimbursement may impact the demand for, or the price of, any product for which we obtain marketing approval. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with products administered under the supervision of a physician. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate that we successfully develop.

There may be significant delays in obtaining reimbursement for approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or regulatory authorities in other countries. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the product and the clinical setting in which it is used, may be based on payments allowed for lower cost products that are already reimbursed and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of products from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government funded and private payors for our existing or new products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Healthcare reform measures could hinder or prevent the commercial success of our products or our product candidates.

In the United States, there have been and we expect there will continue to be a number of legislative and regulatory changes to the healthcare system in ways that could affect our future revenue and profitability and the future revenue

and profitability of our potential customers. Federal and state lawmakers regularly propose and, at times, enact legislation that would result in significant changes to the healthcare system, some of which are intended to contain or reduce the costs of medical products and services. For example, one of the most significant healthcare reform measures in decades, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, was enacted in 2010. The Affordable Care Act contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement changes

and fraud and abuse measures, all of which will impact existing government healthcare programs and will result in the development of new programs. The Affordable Care Act, among other things:

- imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell "branded prescription drugs," effective 2011;
- increased the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1% of the "average manufacturer price", effective 2011;
- expanded Medicaid drug rebates to cover drugs paid by Medicaid managed care organizations;
- changed the Medicaid rebate rates for line extensions or new formulations of oral solid dosage form;
- expanded the types of entities eligible for the "Section 340B discounts" for outpatient drugs;
- required manufacturers to participate in a coverage gap discount program, under which they must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable branded drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and
- created a process for approval of biologic therapies that are similar or identical to approved biologics and provides 12 years of regulatory exclusivity for biologics.

Legislative changes to or regulatory changes under the Affordable Care Act remain possible and appear likely in the 116th U.S. Congress and under the current administration. In addition, since January 2017, the President has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act included a provision which repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On January 22, 2018, the President signed a continuing resolution on appropriations for fiscal year 2018 delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018 ("BBA"), among other things, amended the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. While the Texas U.S. District Court Judge, as well as the Presidential administration and the Centers for Medicare & Medicaid Services, or CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business. Moreover, several attempts have been made to reduce the length of exclusivity for biologic therapies, via federal government budget proposals and proposed legislation. For example, the Price Relief, Innovation, and Competition for Essential Drugs ("PRICED") Act, introduced in 2016, would have reduced exclusivity for biological drugs from 12 to seven years. We cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. For example, the Budget Control Act of 2011, or Budget Control Act, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, which triggered the legislation's automatic reduction to several government programs, including aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in April 2013, and due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027 unless additional Congressional

action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced

Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation 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 products. At the federal level, the administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While some of these and other proposed measures may require additional authorization to become effective, Congress and the Presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly 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.

There likely will continue to be legislative and regulatory proposals at the federal and state levels directed at containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future or their full impact. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- our ability to set a price we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability; and
- the availability of capital.

If we fail to comply with healthcare regulations, we could face substantial penalties and our business, operations and financial condition could be adversely affected.

Pharmaceutical companies are heavily regulated by federal, state and local regulations in the countries in which business activities occur. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We could be subject to laws and regulations governing healthcare fraud and abuse, advertising and other promotional activities, data privacy and patient rights by both the federal government and the states in which we conduct our business. The regulations that may affect our ability to operate include, without limitation:

- the federal Anti-Kickback Statute, which prohibits, among other things, any person or entity from knowingly and willfully offering, soliciting, receiving or providing 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;
- the federal Physician Payments Sunshine Act or Open Payments Program provisions and the implementing regulations which will require, among other things, extensive tracking of physician and teaching hospital payments, maintenance of a payments database, and public reporting of the payment data;
- the federal civil False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, false claims, or knowingly using false statements, to obtain payment from the federal government;
-

federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- federal and state laws governing data privacy and the EU general data privacy regulation ("GDPR");
- the Foreign Corrupt Practices Act and similar statutes and regulations in foreign jurisdictions, which makes it unlawful for certain classes of persons and entities to make payments to foreign government officials to assist in obtaining or retaining business;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, and their implementing regulations which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
- the Drug Quality and Security Act which requires manufacturers and other distribution parties to create systems to trace certain prescription drugs as they are distributed in the United States; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state and local laws that require pharmaceutical companies to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; state laws that require the reporting of information related to drug pricing; and state and local laws requiring the registration of pharmaceutical sales and medical representatives.

The Affordable Care Act, among other things, amended the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to substantial penalties, including civil and criminal penalties, damages, fines, possible exclusion from participation in Medicare, Medicaid, and other federal healthcare programs, integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. 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. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly.

The United Kingdom's planned withdrawal from the EU may have a negative effect on our business, global economic conditions, and financial markets.

As a result of the United Kingdom's vote to leave the EU in March 2019, the EMA announced that it will relocate its headquarters from London to Amsterdam by March 30, 2019. Since a significant proportion of the regulatory framework in the United Kingdom is derived from EU directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of product candidates, disrupt the manufacture of our products and product candidates in the United Kingdom or the EU, disrupt the importation and export of active substances and other components of drug formulations, and disrupt the supply chain for clinical trial product and final authorized formulations. While negotiations continue regarding the terms of the United Kingdom's withdrawal from the EU, the specific impact to the supervision, regulation and supply of medicines in the United Kingdom and Europe remain unclear. The cumulative effect of disruptions to the regulatory framework or supply chains may add considerably to the development lead time to, and expense of, marketing authorization and commercialization of products in the EU and/or the United Kingdom. In view of the uncertainty surrounding the Brexit implementation, we are unable to predict the effects of such disruption to the regulatory framework and supply chain in Europe.

7) RISKS RELATED TO OWNERSHIP OF OUR COMMON STOCK

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Our stock price may be volatile, and investors in our common stock could incur substantial losses.

Our stock price has fluctuated in the past and may be volatile in the future. The stock market in general, and the market for biotechnology companies in particular, have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may experience losses on their investment in our stock. The market price for our common stock may be influenced by many factors, including the following:

- the timing and amount of revenues generated from sale of our products or product candidates;
- our ability to meet the expectations of investors related to the commercialization of our products and product candidates;
- regulatory actions or decisions, including the timing and outcome of any potential future FDA or EMA decision, or other products or product candidates, including those of our competitors;
- inaccurate sales or cash forecasting of our products or product candidates;
- changes in laws or regulations;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- results of clinical trials or regulatory actions with respect to our products or product candidates;
- market conditions in the pharmaceutical and biotechnology sectors;
- changes in the structure of healthcare payment systems;
- actual or anticipated changes in earnings estimates or changes in stock market analyst recommendations regarding our common stock, other comparable companies or our industry generally;
- trading volume of our common stock;
- sales of our common stock by us or our stockholders;
- general economic, industry and market conditions; and
- the other risks described in this “Risk factors” section.

These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market, securities class-action litigation has often been instituted against companies. In addition, following our update call on September 5, 2017, at least three plaintiffs’ securities litigation firms publicly announced that they are investigating potential securities fraud claims that they may wish to make against us. Such litigation, if instituted against us, could result in substantial costs and diversion of management’s attention and resources, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, our stock price and trading volume could decline.

The trading market for our common stock depends, in part, on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts may cease to publish research on our company at any time in their discretion. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline. In addition, if one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline. If our operating results fail to meet the forecasts of analysts, our stock price will likely decline.

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Provisions in our corporate charter documents and under Delaware law could make an acquisition of us more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. Among others, these provisions include the following:

- our board of directors is divided into three classes with staggered three-year terms which may delay or prevent a change of our management or a change in control;
- our board of directors has the right to elect directors to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;
- our stockholders may not act by written consent or call special stockholders' meetings; as a result, a holder, or holders, controlling a majority of our capital stock would not be able to take certain actions other than at annual stockholders' meetings or special stockholders' meetings called by the board of directors, the chairman of the board, the chief executive officer or the president;
- our certificate of incorporation prohibits cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;
- stockholders must provide advance notice and additional disclosures in order to nominate individuals for election to the board of directors or to propose matters that can be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company; and
- our board of directors may issue, without stockholder approval, shares of undesignated preferred stock; the ability to issue undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to acquire us.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Our agreements with our executive officers may require us to pay severance benefits to any of those persons who are terminated in connection with a change in control of us, which could harm our financial condition or results or discourage third parties from seeking business combinations.

Our executive officers are parties to agreements that contain change in control and severance provisions providing for aggregate cash payments of up to approximately $6.6 million for severance and other benefits and acceleration of vesting of equity awards with a value of approximately $5.3 million as of December 31, 2018, based on the closing price of our common stock of $19.52 on such date in the event of a termination of employment in connection with a change in control of us. The accelerated vesting of equity awards could result in dilution to our existing stockholders and harm the market price of our common stock. The payment of these severance benefits could harm our financial condition and results. In addition, these potential severance payments may discourage or prevent third parties from seeking a business combination with us.

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Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of existing or any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We lease approximately 74,000 square feet of research and office space in South San Francisco, California under a lease that expires in March 2020. Thereafter, at our option, we may extend the term for an additional three years to March 2023. We believe that our existing facilities are sufficient for our current needs for the foreseeable future.

ITEM 3. LEGAL PROCEEDINGS

We are not currently a party to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

None.

PART II

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

PRICE RANGE OF COMMON STOCK

Our common stock is listed on The Nasdaq Global Select Market under the symbol "PTLA".

On February 15, 2019, the last reported sale price of our common stock as reported on The Nasdaq Global Select Market was $30.96 per share. As of February 15, 2019, there were 66,821,167 shares of our common stock issued and outstanding with 14 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

STOCK PRICE PERFORMANCE GRAPH

The following stock performance graph compares our total stock return with the total return for (i) the Nasdaq Composite Index and the (ii) the Nasdaq Biotechnology Index for the period from May 22, 2013 (the date our common stock commenced trading on the Nasdaq Global Select Market) through December 31, 2018. The figures represented below assume an investment of $100 in our common stock at the closing price of $15.15 on May 22, 2013 and in the Nasdaq Composite Index and the Nasdaq Biotechnology Index on May 22, 2013 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the Securities and Exchange Commission, or SEC, and are not intended to forecast or be indicative of possible future performance of our common stock. This graph shall not be deemed “soliciting material” or be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.