PORTOLA PHARMACEUTICALS INC
Form 424B5
September 11, 2017
Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration Statement No. 333-207901

The information in this preliminary prospectus supplement and the accompanying prospectus is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated September 11, 2017

Preliminary Prospectus Supplement to Prospectus dated November 9, 2015

$300,000,000

Portola Pharmaceuticals, Inc.

Common Stock

We are offering shares of our common stock with an aggregate public offering price of $300,000,000 pursuant to this prospectus supplement. Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. On September 8, 2017, the last reported sale price of our common stock on The NASDAQ Global Select Market was $57.30 per share.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page S-7.

	Per Share	Total
Public offering price	$	$
Underwriting discounts and commissions(1)	$	$
Proceeds, before expenses, to us	$	$

(1) See Underwriting for additional disclosure regarding underwriting discounts, commissions and estimated expenses.

We have granted the underwriters an option to purchase additional shares of our common stock with an aggregate public offering price of up to $45,000,000 at the public offering price, less the underwriting discounts and commissions, within 30 days from the date of this prospectus supplement.

The underwriters expect to deliver the shares against payment in New York, New York on September , 2017.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or accompanying prospectus. Any representation to the contrary is a criminal offense.

Morgan Stanley **Citigroup** **Goldman Sachs & Co. LLC**

Cowen **William Blair**

Prospectus supplement dated September , 2017

Table of Contents

Table of contents

Prospectus supplement

Prospectus

Table of Contents

About this prospectus supplement

This document consists of two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus, gives more general information, some of which may not apply to this offering. If there is a difference between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference, on the other hand, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined.

We have not, and the underwriters have not, authorized anyone else to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, along with the information contained in any permitted free writing prospectuses we have authorized for use in connection with this offering. We take, and the underwriters take, no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus and any authorized free writing prospectus is accurate only as of the date of this prospectus supplement or the date of the accompanying prospectus, and the information in the documents incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date of those respective documents, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates. It is important for you to read and consider all information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus in making your investment decision. You should read this prospectus supplement and the accompanying prospectus, as well as the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, any authorized free writing prospectus, and the additional information described under Where you can find more information in this prospectus supplement and in the accompanying prospectus, before investing in our common stock.

Neither we nor the underwriters have done anything that would permit this offering or possession or distribution of this prospectus supplement and the accompanying prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who come into possession of this prospectus supplement, the accompanying prospectus and any free writing prospectus related to this offering in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement, the accompanying prospectus and any such free writing prospectus applicable to that jurisdiction.

This document has been prepared on the basis that any offer of shares in any relevant European Economic Area member state will be made pursuant to an exemption under European prospectus law from the requirement to publish a prospectus for offers of shares and does not constitute an offer to or solicitation of anyone to purchase shares in any jurisdiction in which such offer or solicitation is not authorized, nor to any person to whom it is unlawful to make such an offer or solicitation.

Unless stated otherwise, references in this prospectus supplement and the accompanying prospectus to the company, Portola, we, us and our refer to Portola Pharmaceuticals, Inc., and its consolidated subsidiary.

This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectuses we have authorized for use in connection with this offering, include trademarks, service marks and trade names owned by us or others companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectuses we have authorized for use in connection with this offering, are the property of their respective owners.

Table of Contents

Prospectus supplement summary

This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus, and does not contain all of the information that you need to consider in making your investment decision. This prospectus supplement and the accompanying prospectus include information about the shares of common stock that we are offering as well as information regarding our business. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety. You should carefully consider the information set forth under Risk factors beginning on page S-7 of this prospectus supplement before making your investment decision.

Overview

We are a biopharmaceutical company focused on the development and commercialization of novel therapeutics in the areas of thrombosis, other hematologic disorders and inflammation for patients who currently have limited or no approved treatment options. We are advancing three programs, including Bevyxxa® (betrixaban), an oral once-daily anticoagulant Factor Xa, or fXa, inhibitor, andexanet alfa (proposed tradename AndexXa®), a recombinant protein designed to reverse the anticoagulant effect in patients treated with an oral or injectable fXa inhibitor, and cerdulatinib, a spleen tyrosine kinase, or Syk, and Janus kinases, or JAK, inhibitor in development to treat hematologic cancers.

On June 23, 2017, we received marketing approval from the U.S. Food and Drug Administration, or FDA, for Bevyxxa, for the prophylaxis of venous thromboembolism, or 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. The timeline on which we are planning to launch Bevyxxa in the United States is between November 2017 and the end of the first quarter of 2018, although this schedule could be extended depending on regulatory or manufacturing developments. During the pre-launch period, we intend to complete salesforce training, drug manufacturing validation and inventory buildup and hospital and payer negotiations regarding formulary placement. We have established a wholesale acquisition cost, or WAC, price for Bevyxxa of $15 per 80mg or 40mg capsule, or $1,500 per 100 count bottle.

In the United States, France, Germany, Italy, Spain, the United Kingdom and Japan, or the G7 countries, an estimated 24 million acutely ill medical patients are hospitalized each year. 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, or DVT, and pulmonary embolism, or PE, blood clots, 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 fXa inhibitors, is approved for in-hospital and extended VTE prophylaxis in acutely ill medical patients.

Bevyxxa, an oral, once-daily fXa inhibitor, was granted a Fast Track designation and approved by the FDA under Priority Review, which is a status given to drugs that may offer significant improvements in treatment or provide a treatment where no adequate therapy exists. Our Marketing Authorization Application or MAA, for betrixaban to the Committee for Medicinal Products for Human Use of the European Medicine Agency, or EMA, was accepted in December 2016 under a standard review period.

Bevyxxa was approved by the FDA based on data from our pivotal Phase 3 APEX Study, which enrolled 7,513 patients at more than 450 clinical sites worldwide. The APEX study evaluated oral betrixaban for 35 to 42 days

Table of Contents

compared with injectable enoxaparin for 6 to 14 days followed by placebo in assessing the prevention of VTE in high-risk acutely ill medical patients. As detailed in the prescribing information, Bevyxxa efficacy was measured in the modified Intent-to-Treat (mITT) analysis, which includes 7,441 patients assessed by a composite outcome score comprising either the occurrence of asymptomatic proximal DVT or symptomatic DVT, non-fatal PE or VTE-related death. Bevyxxa reduced the incidence of DVT and PE blood clots compared with those taking enoxaparin plus placebo (4.4% for Bevyxxa vs. 6.0% for enoxaparin; relative risk reduction 0.75, 95% CI: 0.61, 0.91) with no significant increase in major bleeding (0.67% for Bevyxxa vs. 0.57% for enoxaparin). The most frequent reason for treatment discontinuation was bleeding, with an incidence rate for all bleeding episodes of 2.4% and 1.2% for betrixaban and enoxaparin, respectively.

We believe Bevyxxa s pharmacoeconomic value is attractive and comparable to those of other recently launched cardiovascular products. One measure of this value is Bevyxxa s ability to reduce the risk of VTE and other serious events, such as heart attacks and strokes, which carry significant economic cost in addition to their impact on individual lives. For example, in the APEX trial, Bevyxxa demonstrated relative risk reductions of 32% in all VTE events, which have an estimated cost of $14,000 to $25,000 per event, 54% in VTE-related deaths and 63% in re-hospitalizations. Bevyxxa also demonstrated a risk reduction in heart attacks, strokes and intracranial hemorrhages, which have an estimated cost of $30,000 to $50,000 per event. The typical cost of a course of therapy with Bevyxxa is under $600. To compare Bevyxxa s pharmacoeconomic value against those of other products, we analyzed data from the APEX trial for Bevyxxa and published clinical trial data for Eliquis® for the prevention of stroke in patients with atrial fibrillation, Entresto for the prevention of hospitalization in patients with chronic heart failure and Repatha for the prevention of stroke and myocardial infarction in patients with hypercholesterolima. In each case, based on clinical trial results, we estimated the cost to give each therapy to a population of patients and divided by the number of serious medical events prevented in that population to calculate an estimated cost per event avoided, or saved. Bevyxxa s cost per event saved was $33,600, while the cost per event saved for the other three therapies ranged from $450,000 to approximately $2.0 million.

Our second lead compound, andexanet alfa, an FDA-designated breakthrough therapy and orphan drug, is a recombinant protein designed to reverse anticoagulant activity in patients treated with an fXa inhibitor. Andexanet alfa has potential indications for patients anticoagulated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed, such as in life-threatening or uncontrolled bleeding or for emergency surgery or urgent procedures. We have completed Phase 3 registration studies in healthy volunteers and are conducting a Phase 4 confirmatory trial in patients. We submitted a Biologics License Application, or BLA, to the FDA in the first quarter of 2016 and received a Complete Response Letter, or CRL, in August 2016. In August 2017, we resubmitted our BLA to the FDA in an effort to resolve the items identified by the FDA in the CRL and obtain approval. On August 15, 2017, the FDA notified us that our resubmitted BLA was acceptable for review and assigned it an action due date of February 3, 2018. The BLA seeks initial approval of andexanet alfa for reversal of the anticoagulant effects of apixaban and rivaroxaban in patients experiencing uncontrolled or life-threatening bleeding. We also filed an MAA with the EMA in the third quarter of 2016, which has been accepted and is currently under review. At the same time, we continue to advance our generation 2 manufacturing process that is designed to enable us to produce commercial quantities of andexanet alfa.

Our third product candidate, cerdulatinib, is an orally available dual kinase inhibitor that inhibits Syk and JAK, enzymes that regulate important signaling pathways. Cerdulatinib is being developed for hematologic, or blood, cancers and inflammatory disorders. We are currently conducting a Phase 2a proof-of-concept study for cerdulatinib in patients with non-Hodgkin s lymphoma, or NHL, or chronic lymphocytic leukemia, or CLL, who have failed or relapsed on existing marketed therapies or products in development, including patients with identified mutations. We are currently enrolling patients in the Phase 2a study evaluating the safety and efficacy of cerdulatinib in patients with relapsed/refractory B-cell malignancies who have failed multiple therapies. On June 15, 2017, we announced the

presentation of the interim results of this Phase 2a study demonstrating evidence of efficacy of cerdulatinib in patients with CLL, follicular lymphoma, and peripheral T cell lymphoma.

Table of Contents

In addition to our three lead product candidates, we have other early research and development programs, including a collaboration with Ora Inc. for the development of Syk-selective inhibitors for allergic conjunctivitis and an exclusive in-license agreement with SRX Cardio LLC to explore a novel approach to develop a drug in the field of hypercholesterolemia.

Our strategy

Our goal is to build an enduring biopharmaceutical company with a foundation of products and product candidates that significantly advance patient care in the areas of thrombosis, other hematologic disorders and inflammation. Key elements of our strategy are as follows:

- commercialize Bevyxxa in the United States and, if approved by the EMA, in Europe using a hospital-focused sales force;
- advance andexanet alfa in the United States and European Union through an expedited development and approval process and commercialize it, if approved, using the Bevyxxa sales force;
- advance cerdulatinib for treatment of hematologic cancers; and
- deploy capital strategically to develop and commercialize our portfolio of product candidates.

Financial overview

Our revenue to date has been generated primarily from collaboration and license revenue pursuant to our collaboration agreements including our agreements with Bristol-Myers Squibb Company and Pfizer Inc., Daiichi Sankyo, Bayer Pharma AG, or Bayer, and Janssen Pharmaceuticals, Inc. s and Bayer. We have not generated any commercial product revenue and have continued to incur operating losses. Our operating expenses increased from 2015 through 2016, and we expect that they will continue to increase in 2017 and beyond as we accelerate our efforts to commercialize our oral fXa inhibitor, Bevyxxa, obtain regulatory approval of and commercialize our fXa inhibitor antidote, andexanet alfa, and advance our development pipeline. As of June 30, 2017, we had $269.7 million of cash, cash equivalents and investments which, excluding the net proceeds from this offering, we believe to be sufficient to meet our projected operating requirements into the first quarter of 2018.

Risks associated with our business

Our business is subject to numerous risks and uncertainties related to our financial condition and need for additional capital, the development and commercialization of our product candidates, our reliance on third parties, the operation of our business, our intellectual property, government regulation and this offering and ownership of our common stock. These risks include those highlighted in the section entitled Risk factors immediately following this prospectus summary, including the following:

we have only one product approved for sale, have not yet offered that or any other product for sale and expect to incur substantial and increasing losses for the foreseeable future;

our success depends heavily on the launch and successful commercialization of our sole approved product, Bevyxxa, and the approval and successful commercialization of our product candidate, andexanet alfa;

we will not be able to launch Bevyxxa until we have produced a sufficient quantity of inventory using a validated commercial manufacturing process;

we are in the early stages of developing our sales or marketing infrastructure and have limited to no history of selling, marketing or distributing therapeutic products;

we rely on third-party contract manufacturing organizations to manufacture and supply Bevyxxa and our product candidates, and a failure of one of our suppliers or manufacturers to perform adequately or

Table of Contents

fulfill our needs could cause delays in commercialization or the development of our product candidates or require us to incur significant costs and devote significant efforts to find new suppliers or manufacturers;

the Complete Response Letter we received with respect to our BLA for andexanet alfa will delay the commercial launch of andexanet alfa and required us to re-submit the BLA with additional information requested by the FDA, and it presents additional risk that andexanet alfa will not be approved by regulatory authorities. Although the FDA has indicated that our resubmitted BLA for andexanet alfa is acceptable for review and assigned it an action due date of February 3, 2018, we can offer no assurances that the resubmission will resolve all items raised in the CRL to the satisfaction of the FDA or that the FDA will not raise previously unidentified issues;

we have narrowed the indications for which we are seeking initial approval of andexanet alfa, which will reduce the number of patients for whom andexanet alfa is indicated, if approved, and will reduce the size of the anticipated market and our financial prospects unless we are successful in obtaining approval for an expanded label over time;

our operating results may fluctuate significantly, are difficult to predict and could fall below expectations;

we may need additional funds to support our operations, and such funding may not be available on acceptable terms or at all;

our inability to promptly obtain coverage and profitable payment rates from both government funded and private payers for Bevyxxa or new products that we develop could have a material adverse effect on us;

clinical studies are costly and time consuming, and if they fail to demonstrate safety and efficacy to the satisfaction of the FDA or similar regulatory authorities, we may be unable to commercialize our product candidates;

if serious adverse side effects are identified during the development or commercialization of any of our product candidates or Bevyxxa, we may need to abandon our development or commercialization of that product candidate or product;

we are only allowed to market our approved products for the specific indication for which they receive approval, which for our product candidates may be more limited than we currently anticipate;

we face substantial competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies;

our product candidates have never been manufactured on a commercial scale, and there are risks associated with scaling up manufacturing to commercial scale;

our business may be adversely affected if we are unable to obtain and maintain effective intellectual property rights or fail to comply with our obligations in our intellectual property licenses with third parties; and

our stock price may be volatile, and purchasers of our common stock could incur substantial losses.

Company Information

We were incorporated in Delaware in September 2003. Our principal executive offices are located at 270 E. Grand Avenue, South San Francisco, California 94080, and our telephone number is (650) 246-7000. Our website address is *www.portola.com*. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus supplement, the accompanying prospectus, or any free writing prospectus, and you should not consider it part of this prospectus supplement or accompanying prospectus or free writing prospectus. Our website address is included in this document as an inactive textual reference only.

Table of Contents

The offering

Common stock offered by us	Shares of our common stock with an aggregate public offering price of $300,000,000.
Common stock to be outstanding immediately after this offering	shares, or shares if the underwriter s option to purchase additional shares is exercised in full.
Underwriters option	The underwriters have an option to purchase additional shares of our common stock with an aggregate public offering price of up to $45,000,000, which they may exercise, in whole or in part, for a period of 30 days from the date of this prospectus supplement.
Use of proceeds	The net proceeds from the issuance of our common stock in this offering will be approximately $ million or approximately $ million if the underwriters exercise their option in full, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use approximately $100 million of the net proceeds from this offering to support the commercial launches of Bevyxxa and andexanet alfa in the United States, which would include the build out of a commercial organization, including support functions, as well as marketing support and promotional activities. We intend to use approximately $150 million of the net proceeds from this offering to fund commercial manufacturing in order to attain the strategic inventory levels necessary to sustain product availability for Bevyxxa and andexanet alfa. We intend to use approximately $50 million of the net proceeds from this offering to conduct clinical trials, including ANNEXA-4, and to fulfill regulatory commitments for Bevyxxa and andexanet. We expect to use the balance of the funds for the completion of the cerdulatinib Phase 1/2a study, additional research activities, initial activities related to European launches, working capital, capital expenditures and other general corporate purposes, which may include the acquisition or licensing of other products, businesses or technologies and additional early stage research and development activities. See Use of proceeds for additional information.
Risk factors	See Risk factors beginning on page S-7 and the other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors you should

carefully consider before deciding to invest in our common stock.

NASDAQ Global Select Market symbol	PTLA

Table of Contents

The number of shares of our common stock to be outstanding after this offering is , based on 57,821,438 shares of our common stock outstanding as of September 8, 2017, and excludes the following as of that date:

- 7,563,045 shares of our common stock issuable upon the exercise of stock options, at a weighted-average exercise price of $29.75 per share, and under restricted stock units;
- 3,627,870 shares of our common stock reserved for future issuance under our 2013 Equity Incentive Plan;
- 1,611,807 shares of our common stock reserved for future issuance under our 2013 Employee Stock Purchase Plan;
- 1,166,000 shares of our common stock reserved for future issuance under our Inducement Plan;
- 1,500 shares of our common stock issuable upon the exercise of common stock warrants, at a weighted-average exercise price of $13.10 per share; and
- shares with a value of up to $30 million that may be issued under an agreement with one of our contract manufacturers.

Unless otherwise indicated, all information in this prospectus supplement reflects and assumes no exercise of the underwriters option to purchase additional shares of our common stock.

Table of Contents

Risk factors

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, together with all the other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus before making an investment decision. The risks described below are not the only ones facing our company. Additional risks not presently known to us or that we currently deem immaterial may also impair our business operations. Our business, financial condition or results of operations could be materially and adversely affected by any of these risks. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks related to our financial condition and need for additional capital

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

We are an early stage commercial biopharmaceutical company preparing to launch our first commercial product. Bevyxxa is our only approved product, and we continue to continue incur significant expenses related to the planned commercialization of Bevyxxa, the funding of our ongoing and planned future clinical studies and other research and development activities, and selling, general and administrative activities. Our operating expenses increased during the second quarter of 2017 and we expect that they will continue to increase in the second half of 2017 and beyond. As of June 30, 2017, we had an accumulated deficit of approximately $1.0 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, the 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 the benefit of tax credits made available under a federal stimulus program supporting drug development. We have devoted substantially all of our efforts to research and development, including 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 Bevyxxa and other products for which we may obtain regulatory approval, including process improvements in order to manufacture andexanet alfa at commercial scale;
- initiate or continue clinical studies of betrixaban and our two most advanced product candidates;
- 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 Bevyxxa and developing and commercializing other products with significant market potential. This will require us to be successful in a range of activities, including advancing our product candidates, completing clinical studies of our product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling Bevyxxa and those products for which we may obtain regulatory approval. 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.

Table of Contents

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 Bevyxxa and the absence of historical sales data, Bevyxxa sales will be difficult to predict from period to period and as a result, you should not rely on Bevyxxa sales results in any period as being indicative of future performance and sales of Bevyxxa 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 relating to Bevyxxa, and andexanet alfa and cerdulatinib if approved, including:

- the level of demand;
- 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 payers;
- 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 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; and
- expenditures that we will or may incur to acquire or develop additional technologies, product candidates and products.

In addition, from time to time, we enter into collaboration agreements with other companies that include development funding and upfront and milestone payments, and we expect that amounts earned from our collaboration agreements will continue to be an important source of revenue. These upfront and milestone payments may vary significantly from quarter to quarter and any such variance could cause a significant fluctuation in our operating results from one quarter to the next.

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 may 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 or require us to relinquish rights to our product candidates and technologies.

We are preparing to launch commercial operations for our first product and advancing multiple product candidates through the research and clinical development process. The completion of development and commercialization of Bevyxxa or our product candidates will continue to require substantial funds. As of

Table of Contents

June 30, 2017, we had $269.7 million in cash, cash equivalents and investments which, excluding the net proceeds from this offering, we believe to be sufficient to meet our projected operating requirements into the first quarter of 2018. Our future financing requirements will depend on many factors, some of which are beyond our control, including the following:

- the costs of commercialization activities, including product sales, marketing, manufacturing and distribution and general corporate and commercial infrastructure;
- 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 future 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. 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.

Risks related to the commercialization of Bevyxxa and the development and commercialization of our product candidate

Our success depends heavily on the launch and commercialization of Bevyxxa and the approval and successful commercialization of our product candidate andexanet alfa. Our commercialization and development of andexanet alfa and our other product candidates may not be successful. If we are unable to commercialize one or more of our product candidates, or experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources into the development and commercialization of Bevyxxa, the development of andexanet alfa and, to a lesser extent, cerdulatinib and our selective Syk inhibitor program. Our ability to generate product revenue from Bevyxxa or from our product candidates, which will not occur until after regulatory approval, if ever, will depend on the successful development, regulatory approval and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- our ability to reach agreement with the FDA and other regulatory authorities on the appropriate regulatory path for approval of our product candidates;

Table of Contents

receipt of marketing approvals from the FDA and similar regulatory authorities outside the United States for our product candidates;

obtaining product indications and other labeling information that is acceptable to the medical community, third-party payers and patients;

our ability to manufacture product commercially at acceptable costs;

acceptance of any approved product by the medical community, third-party payers and patients;

establishing and maintaining commercial manufacturing arrangements with third parties;

commercializing any product candidate that may be approved, whether alone or in collaboration with others;

effectively competing with other therapies;

a continued acceptable safety profile of the product following approval;

successful enrollment in, and completion of, clinical studies; and

obtaining, maintaining, enforcing and defending intellectual property rights and claims.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

We will not be able to launch Bevyxxa until we have produced a sufficient quantity of inventory using a validated commercial manufacturing process.

We are still in the process of validating our commercial manufacturing process for Bevyxxa. This validation is taking longer than planned because the material produced by our contract manufacturer to date for commercial inventory does not conform to the current product release specification since it contains measurable quantities of a known crystal polymorphic variant. We are seeking to address this nonconformity through two different means. First, in July 2017, we formally sought FDA approval to modify the release specification to permit Bevyxxa drug substance to contain up to a specified percentage of the polymorphic variant. The FDA is currently reviewing this request under a four-month review process and has assigned it an action due date of November 28, 2017. Second, we have initiated a new manufacturing campaign at our contract manufacturer using a slightly different manufacturing process that in the past has consistently produced material that would conform to the current release specification. We will need to seek and obtain FDA approval for the use of this process for commercial manufacturing. The FDA could assign a four- or six- month review process for this application. If the FDA timely approves our proposed release specification change or we successfully manufacture sufficient conforming inventory using the modified process and the FDA timely

approves the process, then we anticipate commercial launch of Bevyxxa between November 2017 and the end of the first quarter of 2018. However, we cannot give assurance that either or both of these efforts will be successful. If the FDA declines to approve our proposed release specification change, or that approval is significantly delayed, and our parallel manufacturing campaign fails to produce sufficient conforming inventory or is not timely approved by the FDA, the commercial launch of Bevyxxa would be further delayed, and this delay could be significant. A significant delay in the commercial launch of Bevyxxa could materially adversely affect our business, financial condition, results of operations and growth prospects.

Bevyxxa and potential future product candidates may fail to achieve the degree of market acceptance by physicians, patients, healthcare payers and others in the medical community necessary for commercial success.

The commercial success of Bevyxxa and any potential future product candidates for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by the

Table of Contents

medical community and third-party payers 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 product candidates;
- differing interpretations of the results of our clinical trials;
- the willingness of physicians to change their current treatment practices;
- the willingness of hospitals and hospital systems to include our product candidates 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 strength of marketing and distribution support; and
- the availability of third-party coverage or reimbursement.

Failure to attain market acceptance among the medical community and third-party payers may have an adverse impact on our operations and profitability. Although certain of our employees have commercialization experience, as a company we currently have only limited commercial capabilities. We may not be able to attract and retain qualified personnel to serve in our sales and marketing organization to effectively support our commercialization activities. If we are not successful in commercializing Bevyxxa or current or potential future product candidates in the event they receive regulatory approval, our future product revenue will suffer and we may incur significant additional losses.

We currently have limited sales and distribution personnel and are in the initial stages of developing marketing capabilities for Bevyxxa. 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 Bevyxxa, or andexanet alfa and our other future products.

We are in the early stages of developing our sales and marketing infrastructure and have limited to no history of selling, marketing or distributing therapeutic products. To achieve commercial success for Bevyxxa 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 establish a hospital-based sales force in the United States and possibly other major markets and work with partners in other parts of the world to commercialize Bevyxxa globally, and andexanet alfa if it is approved. There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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.

Table of Contents

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 Bevyxxa and developing our current product candidates, and 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. For example, 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, many 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 payers. 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, an indirect Factor Xa inhibitor. Enoxaparin is widely accepted by physicians, patients and third-party payers. As a result, we may face difficulties in marketing Bevyxxa as a substitute therapy in the hospital for the current standard of care, enoxaparin.

Furthermore, the FDA has already approved a number of therapies that, like Bevyxxa, are oral direct fXa inhibitors and that have already achieved substantial market acceptance. Although these products have not been approved for VTE prophylaxis in acutely ill medical patients, the owners of the products may decide to seek such approval or physicians may decide to prescribe these products for the treatment of VTE in acutely ill medical patients absent such approval, known as prescribing off-label. Further, 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, even in cases where they have previously run clinical trials that have failed. For example, in March 2014, Bayer and Janssen announced the initiation of a new Phase 3 clinical trial to evaluate the safety and efficacy of rivaroxaban to reduce the risk of post-hospital discharge symptomatic VTE in patients hospitalized for acute medical illness.

While there are no therapies approved specifically as antidotes for fXa inhibitors, we are aware of at least one drug candidate that has been studied in early stage clinical trials as a potential antidote to fXa inhibitors. In addition, in December 2014, Bristol-Myers Squibb Company and Pfizer Inc. announced that a clinical trial of 15 healthy human subjects demonstrated that two 4-factor prothrombin complex concentrates reversed the steady-state pharmacodynamic effects of Eliquis (apixaban) in several coagulation assessments. Andexanet alfa, if approved, may compete with other currently approved treatments designed to enhance coagulation, such as fresh frozen plasma, prothrombin complex concentrates, recombinant Factor VIIa or whole blood. Although there is no clinical evidence supporting the use of such treatments in patients taking fXa 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 fXa inhibitors.

Also, in October 2015, Boehringer Ingelheim Corporation obtained FDA and EMA approvals of idarucizumab for the reversal of the anticoagulant effect of Pradaxa (dabigatran) for emergency/urgent procedures or in life-threatening or

uncontrolled bleeding. Although idarucizumab is a specific reversal agent for Pradaxa, a direct thrombin inhibitor, rather than a fXa inhibitor, to the extent the availability of a specific reversal agent leads to increased adoption of Pradaxa rather than fXa inhibitors or low molecular weight heparins, the demand for andexanet alfa as a specific reversal agent for fXa inhibitors and low molecular weight heparins could also be reduced.

Table of Contents

There are also a number of products in clinical development for hematologic cancer, ophthalmological diseases, allergic rhinitis, allergic asthma and other inflammatory 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 received a Complete Response Letter to our initial BLA for andexanet alfa from the FDA and we will need to successfully address deficiencies raised by the FDA in our resubmission.

In August 2016, we received a Complete Response Letter, or CRL, from the FDA regarding our BLA for andexanet alfa. This CRL has delayed the commercial launch of andexanet alfa and required us to re-submit our BLA with additional information requested by the FDA, and it may present additional risk that andexanet alfa will not be approved by the FDA or other regulatory authorities, including the EMA. In the CRL, the items raised by the FDA primarily related to the manufacturing process and analytical testing of andexanet alfa. The FDA also asked us for additional data to support the inclusion of edoxaban and enoxaparin in the label and indicated that it needs to finalize its review of the clinical studies required as post-marketing commitments. In August 2017 we resubmitted our BLA to the FDA in an effort to resolve the items identified by the FDA in the CRL and obtain approval of our BLA. On August 15, 2017, the FDA notified us that our resubmitted BLA was acceptable for review and assigned it an action due date of February 3, 2018. We can offer no assurances that the resubmission will resolve all items raised in the CRL to the satisfaction of the FDA or that the FDA will not raise previously unidentified issues. As a result, our ability to market, sell, distribute, obtain acceptable reimbursement for, set pricing for, and continue to operate, commercialize or continue the development of andexanet alfa may be further delayed, adversely affected or prevented altogether.

Even if the outstanding items identified in the CRL are resolved to the satisfaction of the FDA by our resubmission, the agency retains the right not to approve the BLA or to require additional information, or to raise additional issues to support regulatory approval of andexanet alfa, which could further delay or prevent its approval or limit the approved indications for andexanet alfa. In addition, either the substance of the items identified by the FDA in the CRL, or the CRL itself, could have an adverse impact on our efforts to obtain marketing authorization for andexanet alfa from the EMA and other regulatory authorities. Also, in response to the CRL, we have suspended our efforts to expand post-approval supply based on an expanded generation 1 manufacturing process on the 6x2,000 liter Line C manufacturing line at CMC Biologics and are focusing our efforts on expanding post approval through our generation 2 manufacturing process at the 10,000 liter scale at Lonza. As a result, even if we obtain commercial marketing approval for andexanet alfa, our ability to market andexanet may be adversely impacted by limited supply.

Table of Contents

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 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.

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

Table of Contents

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.

The outcome of preclinical testing and early clinical studies may not be predictive of the success of later clinical studies, and interim results of a clinical study do not necessarily predict final results. For example, the favorable results from our Phase 2 proof-of concept studies of andexanet alfa, evaluating the effect of andexanet alfa in healthy volunteers taking apixaban, rivaroxaban, edoxaban or enoxaparin may not be predictive of success in our Phase 4 study or other later studies, if any. In addition, although part 1 of each of our Phase 3 ANNEXA-A (apixaban) and ANNEXA-R (rivaroxaban) studies demonstrated that, for the primary efficacy endpoint, an intravenous bolus of andexanet alfa immediately and significantly reversed the anticoagulation activity of apixaban and rivaroxaban, and part 2 of each of our ANNEXA-A and ANNEXA-R studies demonstrated that, for all the primary and secondary endpoints, an intravenous bolus of andexanet alfa followed by a continuous two-hour infusion sustained the reversal of anticoagulation activity of apixaban and rivaroxaban, these positive results may not be predictive of success in our ANNEXA-4 confirmatory study in certain patients receiving apixaban, rivaroxaban, edoxaban or enoxaparin who present with acute major bleeding. Further, the ANNEXA-4 clinical trial summary data published in August 2016 may not be predictive of the results of the complete ANNEXA-4 trial. We also do not know how the results from our ANNEXA trials will translate into clinical use in patients or the effect of repeat doses. Finally, the favorable interim results from our Phase 2a proof-of-concept study for cerdulatinib in patients with NHL, or CLL, who have failed or relapsed on existing marketed therapies or products in development, including patients with identified mutations, may not be confirmed in future clinical studies or predictive of final results.

If serious adverse side effects are identified with respect to any of our product candidates or our approved product, 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. There can be no assurance that our clinical studies will not fail due to safety issues. In such an event, we might need to abandon development of that product candidate or enter into a partnership to continue development.

For example, Bevyxxa, like all currently marketed inhibitors of fXa, carries some risk of life-threatening bleeding. In addition, patients taking betrixaban 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.

While no serious adverse side effects have been observed in our completed healthy patient studies with andexanet alfa, there is a risk that adverse side effects could be observed through our ANNEXA-4 patient study results, additional clinical experience or repeat doses that are determined to have been caused by andexanet alfa. 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 andexanet alfa or antibodies to fXa 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, reversing the anticoagulant activity of fXa inhibitors in patients with underlying medical conditions requiring anticoagulation is associated with an increased risk of thrombotic events.

Even for Bevyxxa or any of our product candidates that may receive marketing approval, if a regulatory agency discovers adverse events of unanticipated severity or frequency it may impose restrictions on that product or us,

Table of Contents

including requiring withdrawal of the product from the market. Among other legal and administrative actions, a regulatory agency may:

- mandate modifications to 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 payers.

Delays in the enrollment of patients in any of our clinical studies could increase our development costs and delay completion of our clinical studies and associated regulatory submissions.

We may not be able to initiate or continue clinical studies for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these studies as required by the FDA or other regulatory authorities. Even if we are able to enroll a sufficient number of patients in our clinical studies, if the pace of enrollment is slower than we expect, the development costs for our product candidates may increase, and the completion of our studies may be delayed or our studies could become too expensive to complete.

For example, the ANNEXA-4 study of andexanet alfa is our first experience in patients with major bleeding who are receiving a fXa inhibitor. Because we have limited first-hand enrollment experience in this patient population, our enrollment forecasts are estimated based on our understanding of enrollment experience of similar studies conducted by others in similar patient populations. Our current forecasts suggest that enrolling up to 350 patients should ensure that a sufficient number are able to be included in the primary analysis. However, if after enrolling 350 patients, the true number of evaluable patients is less than required, it may be necessary to continue enrolling additional patients beyond the planned 350. Enrollment of additional patients (or slower than anticipated enrollment) could increase the cost and duration of the study, and could result in alterations of the clinical plan including, but not limited to, opening of additional sites or geographic regions, both of which would result in increased costs. In addition, our cerdulatinib clinical studies will require enrollment of patients who have failed current therapies or have relapsed due to mutations. Finding and enrolling a sufficient number of patients for our expansion Cohorts could be difficult, time consuming and expensive because enrollment of clinical patients in the oncology space is often highly competitive and we have limited experience enrolling oncology patients in clinical trials.

Even if andexanet alfa is approved by the FDA, this approval may be limited to certain indications, additional clinical studies and regulatory applications may be required to expand andexanet alfa indications and we can provide no assurances that such additional clinical studies or regulatory applications will be successful.

We are developing andexanet alfa as a universal antidote for patients receiving a fXa inhibitor anticoagulant when reversal of anticoagulation is needed, such as in life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures. Our ANNEXA-4 Phase 4 study is being conducted in patients receiving either a direct or indirect fXa inhibitor who present with an acute major bleed, and our ANNEXA Phase 3 registration-enabling studies have been conducted on healthy volunteers. It is not certain at this time which indications, if any, the FDA will approve based on this data. For example, in the CRL, the FDA stated that we have not provided sufficient information to permit labeling of andexanet alfa for safe and effective use for the proposed indication.

Table of Contents

The FDA has also asked us for additional data to support the inclusion of edoxaban and enoxaparin in the label, and indicated it needed to finalize its review of the clinical studies required as post-marketing commitments. These observations in the CRL create greater risk concerning our efforts to obtain U.S. approval for andexanet alfa as a universal antidote for fXa inhibitors as the issues raised and information requested by the FDA have been, and may continue to be, costly and time-consuming to address and generate. As a result of these observations, we have decided to seek our initial approval on a more narrow indication relating to serious bleeds among patients on the two most broadly used fXa inhibitors, apixaban and rivaroxaban. Our studies have also not included patients requiring emergency surgery or urgent procedures and we do not anticipate obtaining this indication without clinical data. Additional clinical studies will be required to support our targeted indications, which will require additional time and expense and may not prove successful. Limitations in our label for andexanet alfa will reduce the number of patients for whom andexanet alfa is indicated and could reduce the size of the anticipated market and our financial prospects. Further, there is no guarantee that any efforts that we decide to undertake will meet the FDA s requirements, and we may not receive approval at all for andexanet alfa, even in a more narrow indication despite such efforts.

We are seeking regulatory approval of andexanet alfa in the United States through an Accelerated Approval process, and since we have limited experience with this process, the development or commercialization of andexanet alfa could be delayed or abandoned.

In November 2013, the FDA granted breakthrough therapy designation for andexanet alfa, which allows for an Accelerated Approval process. 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 surrogate biomarker endpoint that is considered reasonably likely to predict clinical benefit rather than a clinical endpoint such as survival or irreversible morbidity. Our use of an accelerated approval process requires that our ANNEXA-4 clinical study with clinical endpoints that will correlate to a surrogate endpoint(s) must continue into commercialization, if accelerated approval is granted. Because of the receipt of the CRL, we expect to require more time and incur greater costs than originally anticipated and may not succeed in timely manufacture of drug supply or in obtaining regulatory approval of andexanet alfa. In addition, the FDA may subsequently determine that the studies conducted by us, including any additional studies conducted as a result of the CRL or other FDA responses, were insufficient to support approval for all or some of the marketed direct or indirect fXa inhibitors or proposed indications, or require us to conduct extensive post-approval studies or make modifications to our ongoing ANNEXA-4 study.

There are risks associated with scaling up manufacturing to commercial scale. We will not be able to scale up Bevyxxa manufacturing until our commercial manufacturing process is successfully validated and a second production facility is qualified. Our commercial manufacturing strategy for andexanet alfa is complex and challenging and is subject to increased uncertainty due to the CRL. If our manufacturers are unable to manufacture our products on a commercial scale using validated manufacturing processes or scale to increased production levels, this will likely delay regulatory approval and/or commercialization and materially adversely affect our results of operations and growth prospects.

We are still in the process of validating our commercial process for Bevyxxa manufacturing and qualifying an additional manufacturing facility at our primary supplier. As a part of our commercial scale-up plan, we plan to validate our commercial process at our initial Hovione manufacturing facility and to move commercial production to a different Hovione production facility that has greater manufacturing capacity. Before we can use material manufactured at these facilities, we are required to successfully validate the manufacturing process at the original facility and to demonstrate a successful process transfer and obtain post-marketing regulatory approval for the second facility. We can give no assurance that these efforts will be successful in a timely manner.

There are other risks associated with scaling up manufacturing to commercial volumes including, among others, cost overruns, technical problems with process scale-up, process reproducibility, stability issues, lot consistency,

Table of Contents

regulatory approvals and timely availability of raw materials. There is no assurance that our manufacturers will be able to manufacture our products to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product or to meet potential future demand. If we and our manufacturers are unable to produce sufficient quantities of our products for commercialization, either on a timely basis or at all, our commercialization efforts would be impaired, which would have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We have experienced particular uncertainties and risks associated with scaling up the manufacturing for andexanet alfa. The manufacture of biologics involves complex processes, typically including developing cell lines or cell systems to produce the biologic, growing large quantities of such cells and harvesting and purifying the biologic produced by them. The cost to manufacture biologics is generally far higher than traditional small molecule chemical compounds, and the manufacturing process is more complex and can be difficult to reproduce. Even though we have completed our process validation campaign for generation 2 commercial scale manufacturing, there is no guarantee we will be successful in obtaining regulatory approval for this process. Due to the high cost to manufacture andexanet alfa and the inherent uncertainty related to manufacturing costs, there is a relatively greater risk that andexanet alfa may not be commercially viable.

Our initial commercial manufacturing strategy for andexanet alfa is also subject to substantial uncertainty due to items identified by the FDA in the CRL. Changes to our manufacturing strategy, and addressing the manufacturing items in the CRL, has required and will continue to require additional time and capital and may not be successful. For example, we have suspended our efforts to expand post-approval supply based on an expanded generation 1 manufacturing and are focusing our efforts on expanding supply post-approval through our generation 2 manufacturing process. We still intend to seek commercial approval based on generation 1 supply from CMC Biologics. However, our generation 1 manufacturing process was designed to produce andexanet alfa for our clinical studies on a small scale and is capable of manufacturing only limited supply to support a commercial launch in relation to projected demand. We are currently discussing options with the FDA and our commercial manufacturing organizations for expanding commercial supply post-approval. Without material from an expanded capacity manufacturing facility, even if approved, commercial supply of andexanet alfa at launch will likely be limited to our generation 1 supply until such time as we can the obtain approval for generation 2 material.

In order to obtain FDA approval of generation 2 material produced by Lonza, the vendor s manufacturing facility will need to pass a pre-approval regulatory inspection and we will need to demonstrate that such material is comparable to the clinical material we previously used and material produced in our generation 1 process. Demonstrating comparability can require significant pre-clinical and clinical studies. The material may also be considered a new biological entity and a new clinical program, possibly commencing with Phase 1, and a full BLA submission may be required for approval, resulting in additional time and expense. If we are not able to establish a commercial-scale manufacturing process for andexanet alfa, our business, financial condition, results of operations and growth prospects would be materially adversely affected.

Risks related to our reliance on third parties

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, or 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.

Table of Contents

Moreover, the FDA requires 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 commercialize Bevyxxa or 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 rely on third-party contract manufacturing organizations to manufacture and supply 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 commercial or clinical-scale manufacturing, and we rely on third-party suppliers to manufacture Bevyxxa and our product candidates. For example, we have entered into a manufacturing agreement with Hovione Limited for the manufacture of Bevyxxa and expect to rely on this manufacturing organization to supply Bevyxxa for U.S. commercial launch and, if approved by the EMA, the EU launch. If Hovione fails for any reason to deliver adequate quantities of Bevyxxa, the commercial launch of Bevyxxa will be delayed or disrupted. We have contracted with CMC Biologics to manufacture andexanet alfa bulk drug substance to support our potential U.S. commercial launch, and we have engaged Lonza to develop a new, higher-capacity and lower cost process for andexanet alfa bulk drug substance in order to support our broader, worldwide commercialization strategy. We also rely on other third-party providers for raw materials, drug substance and drug product manufacturing, packaging, labeling and supply chain 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 affected product or product candidate until a qualified alternative supplier is identified, which could also significantly delay or disrupt the development of, and impair our ability to commercialize, our product candidates.

The manufacture of pharmaceutical products in compliance with the FDA s current good manufacturing practices, or cGMPs, 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 cGMP 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 cGMP requirements enforced by the FDA through its facilities inspection program. These requirements include, among other things, quality control, quality

Table of Contents

assurance and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with these cGMP 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 FDA 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 may enter into collaborations that place the development of our 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 outside the United States., or for other purposes. For example, we have out-licensed development and commercial rights to andexanet alfa 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;

Table of Contents

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 would 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.

Risks related to the operation of our business

Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on William Lis, our Chief Executive Officer, and the other principal members of our executive and scientific teams. 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 maintain key person insurance for Mr. Lis but not for any other executives or employees. Any insurance proceeds we may receive under our key person insurance on Mr. Lis would not adequately compensate us for the loss of his services.

Recruiting and retaining other qualified personnel will also be critical to our success. We 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 scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have

commitments under consulting or advisory contracts with other entities that may limit their availability to us.

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 expect to 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

Table of Contents

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 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, 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 against us could cause us to incur substantial liabilities and to limit sales of Bevyxxa and limit commercialization of any other products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical studies, and the manufacturing, distribution and sale of Bevyxxa, and will face an even greater risk if we commercially sell any other products that we may develop. For example, the manufacturers of currently marketed fXa inhibitors and other manufacturers of anticoagulants have faced substantial litigation due to certain alleged bleeding risks. If we cannot successfully defend ourselves against claims that Bevyxxa or our product

Table of Contents

candidates caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for Bevyxxa or any product candidates that we may develop;
- 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 products that we may develop.

We currently hold $10.0 million in product liability insurance coverage, which may not be adequate to cover all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on 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 research programs and product candidates for specific indications. As a result, we may forego or delay pursuit of opportunities with other 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 candidate, we may relinquish valuable rights to that product candidate 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.

Table of Contents

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 products outside 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;

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 Bevyxxa and andexanet alfa development, we are currently utilizing certain suppliers outside of the United States, which subjects us to certain of the above risks.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our drug development programs.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. In particular, the incidence and severity of data theft, ransomware and other forms of computer system hacking have increased significantly in recent years, and biotechnology companies like us have been specifically targeted in many such attacks. While, to our knowledge, we have not experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our 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.

Table of Contents

Risks related to intellectual property

If we fail to comply with our obligations in our intellectual property licenses with 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, one of our selective Syk inhibitors, and our PCSK9 program, 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 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, in which event we may not be able to develop and market any product that is covered by these agreements. Termination of these 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 third parties who license patents to us fail to maintain such patents, or lose rights to those patents, the rights we have licensed 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 which protect our technology or products or which 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. 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. Assuming the other requirements for

patentability are met, prior to March 16, 2013, in the United States, the first to make the claimed invention is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. On March 16, 2013, under the America Invents Act, the United States moved to a first to file system.

Table of Contents

The effects of these changes are currently unclear as the United States Patent and Trademark Office, or USPTO, has only recently implemented various regulations, the courts have only just begun to issue decisions addressing these provisions and the applicability of the act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. We may become involved in opposition or other proceedings challenging our patent rights or the patent rights of others, 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 Pharmaceuticals, Inc., to which we have an exclusive license. The European Patent Office decided in favor of revoking the European patent. Portola has appealed this revocation and we are waiting for final adjudication. This patent is related to a formulation of Bevyxxa. Should the appeal or other proceedings 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. The issuance of a patent is not conclusive as to its 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 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.

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

Competitors 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.

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 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 intellectual property rights with respect to our products 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. If we are found to infringe a third-party s intellectual property rights, we could be

Table of Contents

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. In addition, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our 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.

Table of Contents

Risks related to government regulation

The regulatory approval process is expensive, time consuming and uncertain and may prevent us from obtaining additional approvals for the commercialization 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 FDA also has 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.

Table of Contents

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 United States, 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 European Union, or 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 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 andexanet alfa and betrixaban. To the extent that comparators are available at lower prices than our anticipated pricing for andexanet alfa or betrixaban, 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 Bevyxxa or one or more of our 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 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 payers, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and these third-party payers have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payers are requiring that companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. 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

Table of Contents

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 payers 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 payers 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 payers for Bevyxxa 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.

Failure to obtain regulatory approvals in foreign jurisdictions would prevent us from marketing our products internationally.

We may pursue commercialization of Bevyxxa and our future products in international markets, either through distribution and marketing partners or our own commercial organization. In order to market our future products in the European Economic Area, or 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, or 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.

We have had limited interactions with foreign regulatory authorities, and 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. However, 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.

Healthcare reform measures could hinder or prevent the commercial success of Bevyxxa 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 Affordability 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:

imposes a non-deductible annual fee on pharmaceutical manufacturers or importers who sell branded prescription drugs, effective 2011;

increases the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1%, effective 2011;

Table of Contents

could result in the imposition of injunctions;

expanded Medicaid drug rebates to cover drugs paid by Medicaid managed care organizations;

changes the Medicaid rebate rates for line extensions or new formulations of oral solid dosage form;

expands the types of entities eligible for the Section 340B discounts for outpatient drugs;

requires manufacturers to participate in a coverage gap discount program, under which they must agree to offer 50% 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

creates a process for approval of biologic therapies that are similar or identical to approved biologics.

Legislative changes to or regulatory changes under the Affordable Care Act remain possible and appear likely in the 115th U.S. Congress and under the Trump Administration. The American Health Care Act of 2017, or AHCA, which would repeal and replace key portions of the Affordable Care Act was passed by the U.S. House of Representatives but remains subject to passage by the U.S. Senate. In addition, in January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results and 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 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which delayed for another two months the budget cuts mandated by the sequestration provisions of the Budget Control Act. The ATRA, among other things, also 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. In March 2013, the President signed an executive order implementing sequestration, and in April 2013, the 2% Medicare reductions went into effect. In December 2013, Congress amended the Budget Control Act to provide greater discretionary spending in 2014 and 2015 than originally budgeted and provide relief from the FDA user fee for two years. This amendment also extended the prohibition against reducing payments to Medicare providers by more than 2% until 2023. In December 2014, Congress passed the Consolidated and Further Continuing Appropriations Act, 2015 and a tax extenders bill, both of which may negatively impact coverage and reimbursement of healthcare items and services.

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 payers 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.

Table of Contents

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 payers, 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 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 Payment Sunshine Act or Open Payments Program provisions and the implementing regulations which will require extensive tracking of physician and teaching hospital payments, maintenance of a payments database, and public reporting of the payment data;

- the federal 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;

- 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, 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 payer, including commercial insurers.

The Affordable Care Act, among other things, amends 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 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 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 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.

Table of Contents

Risks related to this offering and ownership of our common stock

Our stock price may be volatile, which could cause investors in our common stock to incur substantial losses and subject us to securities litigation.

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, and we may be subjected to securities litigation. The market price for our common stock may be influenced by many factors, including the following:

- our ability to meet the expectations of investors related to the commercialization of Bevyxxa;
- regulatory actions or decisions affecting Bevyxxa, including the timing and outcome of any potential future FDA or EMA decision relating to Bevyxxa, or other product candidates, including those of our competitors;
- inaccurate sales or cash forecasting of Bevyxxa;
- the timing and amount of revenues generated from sale of Bevyxxa;
- changes in laws or regulations applicable to Bevyxxa;
- announcements by us or our competitors of significant regulatory or commercial developments, acquisitions, strategic partnerships, joint ventures or capital commitments;
- results of clinical trials or regulatory actions with respect to our product candidates;
- market conditions in the pharmaceutical and biotechnology sectors;
- 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.

Table of Contents

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 $3.9 million for severance and other benefits and acceleration of vesting of equity awards with a value of approximately $46.3 million as of June 30, 2017, based on the closing price of our common stock 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.

Table of Contents

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.

Table of Contents

Special note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus, the documents that we have filed with the SEC that are incorporated by reference in this prospectus supplement and accompanying prospectus and any authorized free writing prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our expected uses of the net proceeds to us from this offering;
- our estimates and projections for the clinical development of our product candidates, including clinical research and trials, regulatory approvals and commercial launches, both in the United States and abroad;
- our ability to scale up manufacturing of our approved product and product candidates to commercial scale;
- potential indications for our product candidates;
- our statement regarding the launch, manufacturing and development activities that we expect to be able to complete with our existing capital resources and the net proceeds from this offering;
- our discussion of perceived and projected competitive advantages of our approved product and product candidates;
- the projected patient populations targeted by our product candidates;
- the projected dollar amounts of market opportunities for our approved product and product candidates;
- our ability to successfully commercialize our approved product and product candidates;
- the rate and degree of market acceptance of our approved product and product candidates;
- our ability to successfully build a hospital-based sales force and commercial infrastructure;

our ability to compete with branded and generic fXa inhibitors;

our ability to obtain and maintain intellectual property protection for our products;

the actual receipt and timing of any milestone payments or royalties from our collaborators;

our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;

our ability to identify, develop, acquire and in-license new products and product candidates;

our ability to successfully establish and successfully maintain appropriate collaborations and derive significant revenue from those collaborations;

our financial performance; and

developments and projections relating to our competitors or our industry.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plan, anticipate, believe, estimate, project, predict, potential and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these

uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading Risk factors contained in this prospectus supplement and the accompanying prospectus and in any free writing prospectuses we may authorize for use in connection with this offering, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus supplement and the accompanying prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus supplement, the accompanying prospectus, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Table of Contents

Use of proceeds

The net proceeds from our issuance and sale of shares of our common stock in this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option in full, based on the assumed public offering price of $ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of June 30, 2017, we had available cash, cash equivalents and investments of $269.7 million. We currently estimate that we will use the net proceeds from this offering, together with our cash, cash equivalents and investments, as follows:

- approximately $100 million to support the commercial launches of Bevyxxa and andexanet alfa in the United States, which would include the build out of a commercial organization, including support functions, as well as marketing support and promotional activities;

- approximately $150 million to fund commercial manufacturing in order to attain the strategic inventory levels necessary to sustain product availability for Bevyxxa and andexanet alfa;

- approximately $50 million to conduct clinical trials, including ANNEXA-4, and to fulfill regulatory commitments for Bevyxxa and andexanet alfa; and

- the balance of the funds for the completion of the cerdulatinib Phase 1/2a study, additional research activities, initial activities related to European launches, working capital, capital expenditures and other general corporate purposes, which may include the acquisition or licensing of other products, businesses or technologies and additional early stage research and development activities.

This expected use of the net proceeds from this offering and our existing cash, cash equivalents and investments represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development and commercialization efforts and the status of and results from clinical studies, as well as any collaborations that we may enter into with third parties for our product candidates and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We have no current understandings, agreements or commitments for any material acquisitions or licenses of any products, businesses or technologies.

Based on our planned use of the net proceeds from this offering and our existing cash, cash equivalents and investments described above, we expect that such funds will be sufficient to: launch Bevyxxa and andexanet alfa in both the United States and Europe, manufacture enough commercial product to reach targeted inventory levels in the United States and Europe, enable us to complete our Phase 1/2 proof-of-concept study in non-Hodgkin s lymphoma and chronic lymphocytic leukemia for Cerdulatinib; and continue our Phase 4 confirmatory study for andexanet alfa. However, it is possible that we will not achieve the progress that we expect because the actual costs and timing of drug development, particularly clinical studies, are difficult to predict, subject to substantial risks and delays and often vary depending on the particular indication and development strategy. We do not expect that the net proceeds from this offering and our existing cash, cash equivalents and investments will be sufficient to enable us to fund substantial

development of our other product candidates.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment grade, interest bearing instruments and U.S. government securities.

Table of Contents

Dividend policy

We have never declared or paid, and do not anticipate declaring, or paying in the foreseeable future, any cash dividends on our capital stock. Future determination as to the declaration and payment of dividends, if any, will be at the discretion of our board of directors and will depend on then existing conditions, including our operating results, financial conditions, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Table of Contents

Material United States federal income tax consequences to non-U.S. holders

The following is a summary of the material United States federal income tax consequences to non-U.S. holders (as defined below) of the acquisition, ownership and disposition of our common stock issued pursuant to this offering. This discussion is not a complete analysis of all potential United States federal income tax consequences relating thereto, does not address the potential application of the Medicare contribution tax and does not address any gift tax or estate tax, consequences or any tax consequences arising under any state, local or foreign tax laws, or any other United States federal tax laws. This discussion is based on the Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, judicial decisions and published rulings and administrative pronouncements of the Internal Revenue Service, or IRS, all as in effect as of the date of this prospectus supplement. These authorities may change, possibly retroactively, resulting in United States federal income tax consequences different from those discussed below. We have not requested any ruling from the IRS with respect to the statements made and the conclusions reached in the following summary.

This discussion is limited to non-U.S. holders who purchase our common stock issued pursuant to this offering and who hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all of the United States federal income tax consequences that may be relevant to a particular non-U.S. holder in light of such non-U.S. holder s particular circumstances. This discussion also does not consider any specific facts or circumstances that may be relevant to non-U.S. holders subject to special rules under the United States federal income tax laws, including, without limitation, certain former citizens or long-term residents of the United States, partnerships or other pass-through entities or the investors in such entities, controlled foreign corporations, passive foreign investment companies, corporations that accumulate earnings to avoid United States federal income tax, banks, financial institutions, investment funds, insurance companies, brokers, dealers or traders in securities or commodities, tax-exempt organizations, tax-qualified retirement plans, persons subject to the alternative minimum tax, persons that own, or have owned, actually or constructively, more than 5% of our common stock and persons holding our common stock as part of a conversion transaction or straddle, or a constructive sale, or other risk reduction strategy.

If an entity or arrangement that is classified as a partnership for United States federal income tax purposes holds our common stock, the United States federal income tax treatment of a partner will generally depend on the status of the partner and the activities of the partnership. Partnerships holding our common stock and partners in such partnerships are urged to consult their tax advisors as to particular United States federal income tax consequences to them of holding and disposing of our common stock.

PROSPECTIVE INVESTORS SHOULD CONSULT THEIR TAX ADVISORS REGARDING THE PARTICULAR UNITED STATES FEDERAL INCOME TAX CONSEQUENCES TO THEM OF ACQUIRING, OWNING AND DISPOSING OF OUR COMMON STOCK, AS WELL AS ANY TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL OR FOREIGN TAX LAWS AND ANY OTHER UNITED STATES FEDERAL TAX LAWS OR UNDER ANY APPLICABLE TAX TREATY.

Definition of Non-U.S. Holder

For purposes of this discussion, a non-U.S. holder is any beneficial owner of our common stock that is not a United States person or a partnership (including any entity or arrangement treated as a partnership) for United States federal income tax purposes. A United States person is any of the following:

an individual citizen or resident of the United States;

a corporation (or other entity treated as a corporation for United States federal income tax purposes) created or organized under the laws of the United States, any state thereof or the District of Columbia;

an estate, the income of which is subject to United States federal income tax regardless of its source; or

Table of Contents

a trust (1) whose administration is subject to the primary supervision of a United States court and which has one or more United States persons who have the authority to control all substantial decisions of the trust, or (2) that has a valid election in effect under applicable Treasury Regulations to be treated as a United States person.

Distributions on our Common Stock

If we make cash or other property distributions on our common stock, such distributions will constitute dividends for United States federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under United States federal income tax principles. Amounts not treated as dividends for United States federal income tax purposes will constitute a return of capital and will first be applied against and reduce a non-U.S. holder s tax basis in our common stock, but not below zero. Any excess will be treated as gain realized on the sale or other disposition of our common stock and will be treated as described under the section of this prospectus supplement entitled Gain on Disposition of Our Common Stock below.

Dividends (out of earnings and profits) paid to a non-U.S. holder of our common stock generally will be subject to United States federal withholding tax at a rate of 30% of the gross amount of the dividends, or such lower rate specified by an applicable income tax treaty, subject to the discussion below regarding FATCA. To receive the benefit of a reduced treaty rate, a non-U.S. holder must furnish to us or our paying agent a valid IRS Form W-8BEN or Form W-8BEN-E (or other applicable successor form) including a United States taxpayer identification number and certifying such non-U.S. holder s qualification for the reduced rate. This certification must be provided to us or our paying agent prior to the payment of dividends and must be updated periodically. If the non-U.S. holder holds the stock through a financial institution or other agent acting on the non-U.S. holder s behalf, the non-U.S. holder will be required to provide appropriate documentation to the agent, which then will be required to provide certification to us or our paying agent, either directly or through other intermediaries. Non-U.S. holders that do not timely provide the required certification, but that qualify for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

If a non-U.S. holder holds our common stock in connection with the conduct of a trade or business in the United States, and dividends paid on our common stock are effectively connected with such non-U.S. holder s United States trade or business (and are attributable to such non-U.S. holder s permanent establishment in the United States if required by an applicable tax treaty), the non-U.S. holder will be exempt from United States federal withholding tax. To claim the exemption, the non-U.S. holder must generally furnish a properly executed IRS Form W-8ECI (or applicable successor form).

Any dividends paid on our common stock that are effectively connected with a non-U.S. holder s United States trade or business (and if required by an applicable income tax treaty, are attributable to a permanent establishment maintained by the non-U.S. holder in the United States) generally will be subject to United States federal income tax on a net income basis at the regular graduated United States federal income tax rates in the same manner as if such non-U.S. holder were a resident of the United States. A non-U.S. holder that is a foreign corporation also may be subject to an additional branch profits tax equal to 30% (or such lower rate specified by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year, as adjusted for certain items. Non-U.S. holders should consult their tax advisors regarding any applicable income tax treaties that may provide for different rules.

Distributions on our common stock may also be subject to the discussion regarding backup withholding and FATCA withholding (discussed below).

Table of Contents

Gain on Disposition of our Common Stock

Subject to the discussion regarding backup withholding and FATCA withholding (discussed below), a non-U.S. holder generally will not be subject to United States federal income tax on any gain realized upon the sale or other disposition of our common stock, unless:

- the gain is effectively connected with the non-U.S. holder s conduct of a trade or business in the United States, and if required by an applicable income tax treaty, is attributable to a permanent establishment maintained by the non-U.S. holder in the United States;
- the non-U.S. holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition, and certain other requirements are met; or
- our common stock constitutes a United States real property interest by reason of our status as a United States real property holding corporation, or USRPHC, for United States federal income tax purposes at any time within the shorter of the five-year period preceding the disposition or the non-U.S. holder s holding period for our common stock, and our common stock is not regularly traded on an established securities market during the calendar year in which the sale or other disposition occurs.

The determination of whether we are a USRPHC depends on the fair market value of our United States real property interests relative to the fair market value of our other trade or business assets and our foreign real property interests. We believe we are not currently and do not anticipate becoming a USRPHC for United States federal income tax purposes; however, there can be no assurance that we will not become a USRPHC.

Gain described in the first bullet point above generally will be subject to United States federal income tax on a net income basis at the regular graduated United States federal income tax rates in the same manner as if such non-U.S. holder were a resident of the United States. A non-U.S. holder that is a foreign corporation also may be subject to an additional branch profits tax equal to 30% (or such lower rate specified by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year, as adjusted for certain items.

Gain described in the second bullet point above will be subject to United States federal income tax at a flat 30% rate (or such lower rate specified by an applicable income tax treaty), but may be offset by certain United States-source capital losses (even though the individual is not considered a resident of the United States), provided that the non-U.S. holder has timely filed United States federal income tax returns with respect to such losses.

Non-U.S. holders should consult their tax advisors regarding any applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

We must report annually to the IRS and to each non-U.S. holder the amount of dividends on our common stock paid to such non-U.S. holder and the amount of any tax withheld with respect to those dividends. These information reporting requirements apply even if no withholding was required because the dividends were effectively connected with the non-U.S. holder s conduct of a United States trade or business, or withholding was reduced or eliminated by an applicable income tax treaty. This information also may be made available under a specific treaty or agreement

with the tax authorities in the country in which the non-U.S. holder resides or is established. Unless a non-U.S. holder complies with certification procedures to establish that the non-U.S. holder is not a U.S. person, information returns may also be filed with the IRS in connection with the proceeds from a disposition of our common stock.

Backup withholding, currently at a 28% rate, generally will not apply to payments to a non-U.S. holder of dividends on or the gross proceeds of a disposition of our common stock provided the non-U.S. holder furnishes the required certification as to its non-U.S. status, such as by providing a valid IRS Form W-8BEN, IRS Form W-8BEN-E, IRS Form W-8ECI or other appropriate IRS Form W-8, or certain other requirements are met.

Table of Contents

Notwithstanding the foregoing, backup withholding may apply if the payer has actual knowledge, or reason to know, that the non-U.S. holder is a United States person who is not an exempt recipient. Backup withholding is not an additional tax. If any amount is withheld under the backup withholding rules, the non-U.S. holder should consult with a United States tax advisor regarding the possibility of and procedure for obtaining a refund or a credit against the non-U.S. holder s United States federal income tax liability, if any.

FATCA

Sections 1471 through 1474 of the Code (commonly referred to as FATCA) impose a United States federal withholding tax of 30% on certain payments, including dividends paid on our common stock, made to a foreign financial institution (as specially defined under these rules) unless such institution enters into an agreement with the United States government to withhold on certain payments and to collect and provide to the United States tax authorities substantial information regarding United States account holders of such institution (which includes certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with United States owners) or an exemption applies. FATCA also generally imposes a United States federal withholding tax of 30% on certain payments, including dividends paid on our common stock, made to a non-financial foreign entity unless such entity provides the withholding agent a certification identifying the direct and indirect United States owners of the entity or an exemption applies. An intergovernmental agreement between the United States and an applicable foreign country may modify those requirements. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes. Under certain transition rules, these withholding taxes will also be imposed on gross proceeds from sales or other dispositions of our common stock after December 31, 2018.

Prospective investors are encouraged to consult with their own tax advisors regarding the possible implications of FATCA on their investment in our common stock.

Table of Contents

Underwriting

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC, Citigroup Global Markets Inc. and Goldman Sachs & Co. LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them the number of shares indicated below:

Name	Number of shares
Morgan Stanley & Co. LLC	
Citigroup Global Markets Inc.	
Goldman Sachs & Co. LLC	
Cowen and Company, LLC	
William Blair & Company, L.L.C.	
Total:	

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of $ a share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the underwriters. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters right to reject any order in whole or in part.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter s name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters option to purchase up to an additional shares of our common stock.

		Total	
	Per share	No exercise	Full exercise

Public offering price	$	$	$
Underwriting discounts and commissions to be paid by us:	$	$	$
Proceeds, before expenses, to us	$	$	$

The estimated offering expenses payable by us, exclusive of underwriting discounts and commissions, are approximately $.

Table of Contents

Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA .

We, our directors, and our executive officers have agreed that with the exception of 8,938 shares that may be sold pursuant to existing trading plans pursuant to Rule 10b5-1 of the Exchange Act, without the prior written consent of Morgan Stanley & Co. LLC, we and they will not, during the period ending 90 days after the date of this prospectus supplement (the restricted period):

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock;

- file any registration statement with the SEC relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or

- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of Morgan Stanley & Co. LLC, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- the sale of shares to the underwriters; or

- our issuance of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus supplement and disclosed in this prospectus supplement;

- our issuance of shares or options to purchase shares of our common stock to our employees, officers, directors, advisors or consultants pursuant to employee benefit plans described in this prospectus supplement, provided that, prior to the issuance of any such shares or the grant of any such options, we shall cause each recipient of such grant or issuance to execute and deliver a lock-up agreement;

- our filing of registration statements on Form S-8 with respect to the employee benefit plans described in this prospectus supplement;

the sale or issuance of or entry into an agreement to sell or issue shares of our common stock in connection with our acquisition of one or more businesses, products or technologies (whether by means of merger, stock purchase, asset purchase or otherwise) or in connection with joint ventures, commercial relationships or other strategic transactions; provided, that, the aggregate number of shares of our common stock that we may sell or issue or agree to sell or issue pursuant to this clause shall not exceed 5% of the total number of shares of our common stock issued and outstanding immediately following the closing of our initial public offering and provided further that we shall cause each recipient of such shares to execute and deliver, on or prior to such issuance, a lock-up agreement;

transfers of shares as a bona fide gift, distributions to limited partners, members or stockholders, transfers by will or intestate succession or to any trust or partnership for the benefit of the lock-up signatory or members of the lock-up signatory s immediate family, or the net exercise of stock options issued under our equity incentive plans, provided in each case that (i) each donee, distributee and transferee shall sign and deliver a lock-up agreement to the underwriters and (ii) no filing under Section 16(a) of the Exchange Act shall be required or voluntarily made during the restricted period;

Table of Contents

the establishment or modification of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) no public announcement or filing under the Exchange Act is required of or voluntarily made by or on behalf of the lock-up signatory or us regarding the establishment or modification of such plan; or

the sale of shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock under a trading plan pursuant to Rule 10b5-1 under the Exchange Act that is existing as of the date lock-up agreement and has been disclosed to Morgan Stanley & Co. LLC, provided that to the extent a public announcement or filing under the Exchange Act is required of or voluntarily made by or on behalf of the undersigned or us regarding the sale, such announcement of filing shall include a statement to the effect that the sale occurred pursuant to such trading plan pursuant to Rule 10b5-1.

Morgan Stanley & Co. LLC, in its sole discretion, may release our common stock and other securities subject to the lock-up agreements described above in whole or in part at any time with or without notice.

In order to facilitate the offering of our common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of our common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock on The NASDAQ Global Select Market to stabilize the price of our common stock. The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions. These activities may raise or maintain the market price of our common stock above independent market levels or prevent or retard a decline in the market price of our common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time. Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the underwriters will engage in these stabilizing transactions or that any transaction, once commenced, will not be discontinued without notice.

We and the several underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The underwriters may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory,

Table of Contents

investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. In addition, an affiliate of Cowen and Company, LLC is party to a purchase and sale agreement with us, entered into in February 2017, in which such affiliate acquired a royalty interest in future worldwide sales of andexanet alfa. In connection with the agreement, the affiliate made a $50 million payment to us and may be required to make an additional $100 million payment depending on when and if regulatory approval for andexanet alfa is received. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling restrictions

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive, each, a Relevant Member State, an offer to the public of any shares of our common stock may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an offer to the public in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the

Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

United Kingdom

The underwriters have represented and agree that:

(a) they have only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of

Table of Contents

Section 21 of the Financial Services and Markets Act 2000, or FSMA, received by them in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(b) they have complied and will comply with all applicable provisions of the FSMA with respect to anything done by them in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Canada

The shares of our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of shares of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (**NI 33-105**), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), or (ii) to professional investors within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than

(i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Table of Contents

Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the Financial Instruments and Exchange Law) and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Table of Contents

Legal matters

Cooley LLP will pass upon the validity of the shares of common stock offered hereby. The underwriters are being represented by Davis Polk & Wardwell LLP, Menlo Park, California, in connection with the offering.

Experts

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016, and the effectiveness of our internal control over financial reporting as of December 31, 2016, as set forth in their reports, which are incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our consolidated financial statements are incorporated by reference in reliance on Ernst & Young LLP s reports, given on their authority as experts in accounting and auditing.

Where you can find more information

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any document we file at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference room. The SEC maintains an Internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC, including us. The SEC s Internet site can be found at *http://www.sec.gov*.

Incorporation of certain information by reference

The SEC allows us to incorporate by reference the information we file with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus supplement and the accompanying prospectus. We incorporate by reference the following information or documents that we have filed with the SEC (Commission File No. 001-35935):

- our Annual Report on Form 10-K for the year ended December 31, 2016, which was filed with the SEC on March 1, 2017, or the Form 10-K;
- the information specifically incorporated by reference into the Form 10-K from our definitive proxy statement on Schedule 14A which was filed with the SEC on April 24, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, which was filed with the SEC on May 9, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, which was filed with the SEC on August 9, 2017;

our Current Reports on Form 8-K filed with the SEC on February 3, 2017 (two filings), May 8, 2017 (with respect to the Form 8-K reporting events under Items 5.02 and 9.01 only) , June 19, 2017, and September 11, 2017; and

the description of our common stock in our registration statement on Form 8-A filed with the SEC on May 17, 2013, including any amendments thereto or reports filed for the purposes of updating this description.

Table of Contents

Any information in any of the foregoing documents will automatically be deemed to be modified or superseded to the extent that information in this prospectus or in a later filed document that is incorporated or deemed to be incorporated herein by reference modifies or replaces such information.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until we file a post-effective amendment which indicates the termination of the offering of the securities made by this prospectus supplement and the accompanying prospectus. Information in such future filings updates and supplements the information provided in this prospectus supplement and the accompanying prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Portola Pharmaceuticals, Inc.

270 E. Grand Ave.

South San Francisco, CA 94080

(650) 246-7000

Attn: Secretary

Table of Contents

Prospectus

Common Stock

Preferred Stock

Debt Securities

Warrants

From time to time, we may offer and sell any combination of the securities described in this prospectus, either individually or in combination. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

We will provide the specific terms of these offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered.

Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. On November 6, 2015, the last reported sale price of our common stock was $49.92 per share. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Global Select Market or other securities exchange of the securities covered by the prospectus supplement.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the other documents that are incorporated by reference into this prospectus.

This prospectus may not be used to consummate a sale of securities unless accompanied by a prospectus supplement.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. The supplements to this prospectus will provide the specific

terms of the plan of distribution. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is November 9, 2015.

Table of Contents

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under this shelf registration process, we may offer and sell, either individually or in combination, in one or more offerings, any combination of the securities described in this prospectus. This prospectus provides you with a general description of the securities we may offer.

Each time we offer shares of our securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. We urge you to read carefully this prospectus, any applicable prospectus supplement and any free writing prospectuses we have authorized for use in connection with a specific offering, together with the information incorporated herein by reference as described under the heading Incorporation of Certain Information by Reference, before buying any of the securities being offered.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different or additional information. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

The information appearing in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of

Table of Contents

the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled Where You Can Find More Information.

This prospectus contains and incorporates by reference market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Unless the context otherwise requires, references in this prospectus to the company, Portola, we, us and our refer to Portola Pharmaceuticals, Inc.

Portola Pharmaceuticals, Inc.

Overview

We are a biopharmaceutical company focused on the development and commercialization of novel therapeutics in the areas of thrombosis, other hematologic disorders and inflammation for patients who currently have limited or no approved treatment options. We are advancing our three wholly-owned compounds using novel biomarker and genetic approaches that may increase the likelihood of clinical, regulatory and commercial success of our potentially life-saving therapies. Two of these compounds were discovered through our internal research efforts, and one was discovered by Portola scientists during their time at a prior company.

Our Phase 3 programs address significant unmet medical needs in the area of thrombosis, or blood clots. Betrixaban is a United States Food and Drug Administration, or FDA-designated Fast-Track novel oral once-daily inhibitor of Factor Xa in Phase 3 clinical trial for extended duration prophylaxis, or preventive treatment, of a form of thrombosis known as venous thromboembolism, or VTE, in acute medically ill patients for 35 days of in-hospital and post-discharge use. Currently, there is no anticoagulant approved for extended duration VTE prophylaxis in the acute medically ill population. Our second Phase 3 compound, Andexanet alfa a FDA-designated breakthrough therapy and orphan drug is a recombinant protein designed to reverse the anticoagulant activity in patients treated with a Factor Xa inhibitor. Andexanet alfa has potential indications to reverse anticoagulant activity in patients who are taking a direct or indirect Factor Xa inhibitor and who suffer uncontrolled major bleeding episode or require emergency surgery. We have completed two Phase 3 ANNEXA™ (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) clinical trials one with Bristol-Myers Squibb Company and Pfizer Inc. s, Factor Xa inhibitor, apixaban and one with Bayer Pharma AG and Janssen Pharmaceuticals, Inc. s Factor Xa inhibitor, rivaroxaban. We are currently evaluating Andexanet alfa in a Phase 2 clinical trial with Daiichi Sankyo s Factor Xa inhibitor, edoxaban and our factor Xa inhibitor Betrixaban. We are also currently enrolling patients in a Phase 4 ANNEXA-4 confirmatory study, as agreed to by the FDA and European Medicines Agency, or EMA, as part of an accelerated approval pathway in the United States for Andexanet alfa. Our third product candidate, Cerdulatinib, is an orally available kinase inhibitor that inhibits spleen tyrosine kinase, or Syk, and janus kinases, or JAK, enzymes that regulate important signaling pathways. Cerdulatinib is being developed for hematologic, or blood, cancers and inflammatory disorders. We are currently conducting a Phase 1/2a proof-of-concept study for Cerdulatinib in patients with non-Hodgkin s lymphoma, or NHL, or chronic lymphocytic leukemia, or CLL, who have failed or relapsed on existing marketed therapies or products in development, including patients with identified mutations. In the Phase 1 dose escalation portion of the study, we have yet to reach the maximum tolerated dose and enrollment continues. Based on Phase 1 data, we plan to advance Cerdulatinib to the Phase 2a portion of the study which includes expansion cohorts in select hematologic

cancers. We also have a program of highly selective Syk inhibitors one of which is partnered with Ora Inc.

Table of Contents

Members of our management team, working together or individually, have played central roles at prior companies in discovering, developing and commercializing a number of successful therapeutics in the area of thrombosis, including Integrilin®, Lovenox® and Xarelto®. Our approach has been to identify key enzymes and cellular signaling pathways and to apply our translational expertise to discover compounds with unique properties that have potential for clear clinical and pharmacoeconomic value. To increase the likelihood that our programs will succeed, we enhance our internal discovery and development expertise by collaborating with academic leaders at major universities, including Cornell University, Duke University, Harvard University, King s College, McMaster University, Stanford University and The University of Texas MD Anderson Cancer Center, and by proactively engaging regulatory authorities early in the development process.

We have full worldwide commercial rights to Betrixaban, Andexanet alfa and Cerdulatinib. We believe we can maximize the value of our company by retaining substantial commercialization rights to these three product candidates and, where appropriate, entering into partnerships to develop and commercialize these product candidates. We plan on building a successful commercial enterprise to commercialize Betrixaban and Andexanet alfa globally, using a hospital-based sales team in the United States and possibly other major markets and with partners in other territories.

Company Information

We were incorporated in Delaware in September 2003. Our principal executive offices are located at 270 E. Grand Avenue, South San Francisco, California 94080, and our telephone number is (650) 246-7000. Our website address is *www.portola.com* . Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement or free writing prospectus. Our website address is included in this document as an inactive textual reference only.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in combination, from time to time under this prospectus, together with the applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of any offering. We may also offer common stock, preferred stock and/or debt securities upon the exercise of warrants. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity date, if applicable;
- original issue discount, if any;

rates and times of payment of interest or dividends, if any;

redemption, conversion, exercise, exchange or sinking fund terms, if any;

conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;

Table of Contents

ranking;

restrictive covenants, if any;

voting or other rights, if any; and

material or special U.S. federal income tax considerations, if any.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through agents or underwriters, we will include in the applicable prospectus supplement:

the names of those agents or underwriters;

applicable fees, discounts and commissions to be paid to them;

details regarding over-allotment options, if any; and

the net proceeds to us.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

Common Stock. We may issue shares of our common stock from time to time. The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by our board of directors out of legally available funds. Upon our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption or sinking fund provisions applicable to our common stock. In this prospectus, we have summarized certain general features of the common stock under Description of Capital Stock Common stock. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the designations, voting powers, preferences and rights of the preferred stock, as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the designations, voting powers, preferences and rights of the preferred stock of each series we issue under this prospectus, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will

Table of Contents

file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that contains the terms of the series of preferred stock we are offering. In this prospectus, we have summarized certain general features of the preferred stock under Description of Capital Stock Preferred Stock. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

Any debt securities issued under this prospectus will be issued under one or more documents called indentures, which are contracts between us and a national banking association or other eligible party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under Description of Debt Securities. We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indentures that contain the terms of the debt securities. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Warrants. We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or in combination with common stock, preferred stock and/or debt securities. In this prospectus, we have summarized certain general features of the warrants under Description of Warrants. We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the particular series of warrants being offered, as well as any warrant agreements and warrant certificates that contain the terms of the warrants. We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Any warrants issued under this prospectus may be evidenced by warrant certificates. Warrants also may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

Use of Proceeds

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development, manufacturing, regulatory and commercial related expenses, as well as capital expenditures. See Use of

Proceeds in this prospectus.

Table of Contents

The NASDAQ Global Select Market Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol PTLA. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Global Select Market or any other securities market or other exchange of the securities covered by the applicable prospectus supplement.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks and uncertainties described under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section entitled Risk Factors contained in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also read carefully the section below entitled Special Note Regarding Forward-Looking Statements.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents we have filed with the SEC that are incorporated by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- anticipated timing of results from our Phase 3 clinical study of Betrixaban, or APEX;
- our anticipated timing of our submission of a Biologics License Application and/or a New Drug Application to the FDA;
- our anticipated timing regarding possible commercial launch of our product candidates;
- our commercial strategy for commercial launch of our product candidates;
- the timing and the success of the design of APEX;
- the timing of our Phase 2 proof-of-concept studies of Andexanet alfa;

the timing of our Phase 4 confirmatory study of Andexanet alfa;

our ability to design and implement a registration program of Andexanet alfa in the time frame we project;

whether the results of our APEX study will be sufficient to support global regulatory approvals for Betrixaban;

our ability to obtain and maintain regulatory approval of our product candidates;

the possibility that we will come to an agreement with the FDA for an expedited regulatory approval process for Andexanet alfa;

our ability to conduct a proof-of-concept study in hematologic cancers for Cerdulatinib;

the projected number of acute medically ill patients who would benefit from the use of Betrixaban;

Table of Contents

the projected dollar amounts of future sales of established and novel anticoagulants;

our ability to successfully commercialize our products;

the rate and degree of market acceptance of our products;

our ability to scale up manufacturing of our product candidates to commercial scale;

our ability to successfully build a hospital-based sales force and commercial infrastructure;

our ability to compete with other commercial Factor Xa inhibitors;

our reliance on third parties to conduct our clinical studies;

our reliance on third-party contract manufacturers to manufacture, supply and distribute our product candidates for us;

our reliance on our collaboration partners performance over which we do not have control;

our ability to retain and recruit key personnel;

our ability to obtain and maintain intellectual property protection for our products;

the actual receipt and timing of any milestone payments or royalties from our collaborators;

our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;

our ability to identify, develop, acquire and in-license new products and product candidates;

our ability to successfully establish and successfully maintain appropriate collaborations and derive significant revenue from those collaborations;

our financial performance; and

developments and projections relating to our competitors or our industry.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plan, anticipate, believe, estimate, project, predict, potential and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading Risk Factors contained in the applicable prospectus supplement, in any free writing prospectuses we may authorize for use in connection with a specific offering, and in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus, any applicable prospectus supplement, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Table of Contents

USE OF PROCEEDS

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development, manufacturing, regulatory and commercial related expenses, as well as capital expenditures.

The amounts and timing of our use of the net proceeds from this offering will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any partnering and commercialization efforts, technological advances and the competitive environment for our products. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of the securities offered by us hereunder. Accordingly, our management will have broad discretion in the timing and application of these proceeds. Pending application of the net proceeds as described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments.

RATIO OF EARNINGS TO FIXED CHARGES

The following table sets forth, for each of the periods presented, our ratio of earnings to fixed charges or our deficiency of earnings to cover fixed charges. Our earnings were insufficient to cover fixed charges for the nine months ended September 30, 2015, and the years ended December 31, 2014, 2013 and 2010. The following table sets forth our deficiency of earnings to cover fixed charges for the nine months ended September 30, 2015, and the years ended December 31, 2014, 2013, 2012, 2011 and 2010.

	Nine Months Ended September 30, 2015	Year Ended December 31,				
		2014	2013	2012	2011	2010
			(In thousands, except ratio)			
Ratio of earnings to fixed charges	N/A	N/A	N/A	29:1	48:1	N/A
Deficiency of earnings available to cover fixed charges (in thousands)	$ (160,399)	$ (137,125)	$ (83,352)	$ N/A	$ N/A	$ (17,475)

For purposes of computing the ratio above, earnings consist of (loss) income before income taxes plus fixed charges. Fixed charges include interest expense and the portion of operating lease expense that represents interest.

DESCRIPTION OF CAPITAL STOCK

General

Our amended and restated certificate of incorporation authorizes common stock and authorizes shares of undesignated preferred stock, the rights, preferences and privileges of which may be designated from time to time by our board of

directors.

Our authorized capital stock consists of 105,000,000 shares, all with a par value of $0.001 per share, of which:

- 100,000,000 shares are designated as common stock; and
- 5,000,000 shares are designated as preferred stock.

Table of Contents

Common Stock

Voting rights

Each holder of our common stock is entitled to one vote for each share of common stock held on all matters submitted to a vote of stockholders, except as otherwise expressly provided in our amended and restated certificate of incorporation or required by applicable law. Cumulative voting for the election of directors is not provided for in our amended and restated certificate of incorporation, which means that the holders of a majority of our shares of common stock can elect all of the directors then standing for election.

Economic rights

Dividends and distributions. Subject to preferences that may apply to any shares of convertible preferred stock outstanding at the time, the holders of outstanding shares of our common stock are entitled to receive dividends out of funds legally available at the times and in the amounts that our board of directors may determine.

Liquidation rights. Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock and any participating convertible preferred stock outstanding at that time after payment of liquidation preferences, on any outstanding shares of convertible preferred stock and payment of other claims of creditors.

The rights, preferences, and privileges of holders of our common stock are subject to, and may be adversely affected by, the rights of holders of shares of any series of convertible preferred stock that we may designate and issue in the future.

Preemptive or similar rights. Our common stock is not entitled to preemptive rights and is not subject to conversion or redemption.

Preferred Stock

Our board of directors may, without further action by our stockholders, fix the rights, preferences, privileges and restrictions of up to an aggregate of 5,000,000 shares of preferred stock in one or more series and authorize their issuance. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of our common stock. The issuance of our preferred stock could adversely affect the voting power of holders of our common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change of control or other corporate action. No shares of preferred stock are outstanding, and we have no present plan to issue any shares of preferred stock.

Warrants

As of September 30, 2015, we had three warrants to purchase an aggregate of 1,500 shares of our common stock with an exercise price of $13.10 per share outstanding. Each of these warrants has a net exercise provision under which the holder, in lieu of payment of the exercise price in cash, can surrender the warrant and receive a net number of shares of our common stock based on the fair market value of such stock at the time of exercise of the warrant after deduction of the aggregate exercise price. Unless earlier exercised, these warrants will expire on May 22, 2020.

9

Table of Contents

Anti-takeover provisions

Certificate of incorporation and bylaws

Our amended and restated certificate of incorporation provides for our board of directors to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, our stockholders holding a majority of the voting power of our shares of common stock outstanding will be able to elect all of our directors. The directors may be removed by the stockholders only for cause upon the vote of holders of a majority of the shares then entitled to vote at an election of directors. Furthermore, the authorized number of directors may be changed only by resolution of our board of directors, and vacancies and newly created directorships on our board of directors may, except as otherwise required by law or determined by our board, only be filled by a majority vote of the directors then serving on the board, even though less than a quorum. Our amended and restated certificate of incorporation and amended and restated bylaws provide that all stockholder actions must be effected at a duly called meeting of stockholders and not by a written consent. A special meeting of stockholders may be called only by a majority of our whole board of directors, the chair of our board of directors, our chief executive officer or our president. Our amended and restated bylaws also provide that stockholders seeking to present proposals before a meeting of stockholders to nominate candidates for election as directors at a meeting of stockholders must provide timely advance notice in writing, and will specify requirements as to the form and content of a stockholder s notice.

Our amended and restated certificate of incorporation further provides that the affirmative vote of holders of at least 66 2/3% of the voting power of all of the then outstanding shares of voting stock, voting as a single class, is required to amend certain provisions of our certificate of incorporation, including provisions relating to the structure of our board of directors, the size of the board, removal of directors, special meetings of stockholders, actions by written consent and cumulative voting. The affirmative vote of holders of at least 66 2/3% of the voting power of all of the then outstanding shares of voting stock, voting as a single class, is required to amend or repeal our bylaws, although our bylaws may be amended by a simple majority vote of our board of directors.

The foregoing provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of the company by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of 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 change the control of the company.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of the company. These provisions are also designed to reduce our vulnerability to an unsolicited acquisition proposal and to discourage certain tactics that may be used in proxy rights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of deterring hostile takeovers or delaying changes in control of the company or our management. As a consequence, these provisions also may inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts.

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

Table of Contents

upon closing of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned by (i) persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines business combination to include the following:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loss, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an interested stockholder as an entity or person who, together with the person s affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

Listing

Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The NASDAQ Global Select Market or any securities market or other exchange of the common stock covered by such prospectus supplement.

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust

Table of Contents

Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as discount securities, which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with original issue discount, or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

- the title of the series of debt securities;
- any limit upon the aggregate principal amount that may be issued;
- the maturity date or dates;
- the form of the debt securities of the series;
- the applicability of any guarantees;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;

the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

Table of Contents

if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;

the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder s option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;

the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof;

any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;

whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depositary for such global security or securities;

if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;

if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;

additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;

additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;

additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;

additions to or changes in the provisions relating to satisfaction and discharge of the indenture;

additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;

the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

whether interest will be payable in cash or additional debt securities at our or the holders option and the terms and conditions upon which the election may be made;

the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a United States person for federal tax purposes;

any restrictions on transfer, sale or assignment of the debt securities of the series; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Table of Contents

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;

- if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;

- if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and

- if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable

immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Table of Contents

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request;
- such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

- to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

to comply with the provisions described above under Description of Debt Securities Consolidation, Merger or Sale;

to provide for uncertificated debt securities in addition to or in place of certificated debt securities;

to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;

to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;

to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;

Table of Contents

to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under Description of Debt Securities General to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;

to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or

to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

extending the fixed maturity of any debt securities of any series;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

provide for payment;

register the transfer or exchange of debt securities of the series;

replace stolen, lost or mutilated debt securities of the series;

pay principal of and premium and interest on any debt securities of the series;

maintain paying agencies;

hold monies for payment in trust;

recover excess money held by the trustee;

compensate and indemnify the trustee; and

appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depositary named by us and identified in the applicable prospectus supplement with respect to

Table of Contents

that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we

Table of Contents

initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the internal laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

DESCRIPTION OF WARRANTS

The following description, together with the additional information that we include in any applicable prospectus supplement and in any related free writing prospectus that we may authorize to be distributed to you, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may be issued in one or more series. Warrants may be offered independently or in combination with other securities offered by any prospectus supplement. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements applicable to a particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses, and the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements, that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants being offered, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;

if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;

in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;

Table of Contents

- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

- the terms of any rights to redeem or call the warrants;

- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;

- the dates on which the right to exercise the warrants will commence and expire;

- the manner in which the warrant agreements and warrants may be modified;

- a discussion of any material or special U.S. federal income tax considerations of holding or exercising the warrants;

- the terms of the securities issuable upon exercise of the warrants; and

- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or

- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the close of business on the expiration date set

forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

Upon receipt of payment and the warrant or warrant certificate, as applicable, properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the prospectus supplement, we will, as soon as practicable, issue and deliver the securities purchasable upon such exercise. If less than all of the warrants (or the warrants represented by such warrant certificate) are exercised, a new warrant or a new warrant certificate, as applicable, will be issued for the remaining warrants.

Governing Law

Unless we otherwise specify in the applicable prospectus supplement, the warrants and any warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust

Table of Contents

company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depositary or warrant agent maintain for this purpose as the holders of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as indirect holders of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary s book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its participants. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary s book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in street name. Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are

legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Table of Contents

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depositary participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

Special Considerations For Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

the performance of third party service providers;

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the holders consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

if the securities are in book-entry form, how the depositary s rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under the section entitled Special Situations When a Global Security Will Be Terminated in this prospectus. As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

Table of Contents

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations For Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor s financial institution and of the depositary, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;

an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

the depositary s policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor s interest in a global security;

we and any applicable trustee have no responsibility for any aspect of the depositary s actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depositary in any way;

the depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and

financial institutions that participate in the depositary s book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other

matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in the applicable prospectus supplement, the global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;

Table of Contents

if we notify any applicable trustee that we wish to terminate that global security; or

if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the applicable prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, direct sales to the public, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents or underwriters compensation;

any public offering price;

any discounts or concessions allowed or reallowed or paid to dealers; and

any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallowed or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

Table of Contents

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters or agents that are qualified market makers on The NASDAQ Global Select Market may engage in passive market making transactions in the common stock on The NASDAQ Global Select Market in accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker s bid, however, the passive market maker s bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

Table of Contents

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon for us by Cooley LLP, San Francisco and Palo Alto, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2014, and the effectiveness of our internal control over financial reporting as of December 31, 2014, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our consolidated financial statements are incorporated by reference in reliance on Ernst & Young LLP s reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at http://www.sec.gov. You may also read and copy any document we file at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-35935):

- our Annual Report on Form 10-K for the year ended December 31, 2014, which was filed with the SEC on March 2, 2015 (the Form 10-K);
- the information specifically incorporated by reference into the Form 10-K from our definitive proxy statement on Schedule 14A which was filed with the SEC on April 30, 2015;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, which was filed with the SEC on May 7, 2015;

our Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, which was filed with the SEC on August 5, 2015, as amended by Amendment No. 1 on form 10-Q/A, which was filed with the SEC on August 7, 2015;

Table of Contents

our Quarterly Report on Form 10-Q for the quarter ended September 30, 2015, which was filed with the SEC on November 9, 2015;

our Current Reports on Form 8-K filed with the SEC on January 26, 2015, February 2, 2015, February 10, 2015, March 11, 2015, April 14, 2015, June 18, 2015 and September 25, 2015; and

the description of our common stock in our registration statement on Form 8-A filed with the SEC on May 17, 2013, including any amendments thereto or reports filed for the purposes of updating this description.

Any information in any of the foregoing documents will automatically be deemed to be modified or superseded to the extent that information in this prospectus or in a later filed document that is incorporated or deemed to be incorporated herein by reference modifies or replaces such information.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until we file a post-effective amendment which indicates the termination of the offering of the securities made by this prospectus. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Portola Pharmaceuticals, Inc.

270 E. Grand Ave.

South San Francisco, CA 94080

(650) 246-7300

Attn: Corporate Secretary

Table of Contents