PORTOLA PHARMACEUTICALS INC
Form 424B5
March 10, 2015
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Filed pursuant to Rule 424(b)(5)
Registration Statement No. 333-199094

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 March 9, 2015

Preliminary Prospectus Supplement to Prospectus dated October 1, 2014

2,495,652 Shares

Portola Pharmaceuticals, Inc.

Common Stock

We are offering 2,495,652 shares of our common stock. Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. On March 6, 2015, the last reported sale price of our common stock on The NASDAQ Global Select Market was $41.72 per share.

Investing in our common stock involves a high degree of risk. See Risk factors beginning on page S-8.

	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.

To the extent that the underwriter sells more than 2,495,652 shares of common stock, the underwriter has an option to purchase 374,348 additional shares of common stock from us at the public offering price, after deducting underwriting discounts and commissions.

The underwriter expects to deliver the shares against payment in New York, New York on March , 2015.

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

Prospectus supplement dated March , 2015

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Prospectus supplement

Prospectus

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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 underwriter has 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 underwriter takes, 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 underwriter has 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.

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.

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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-8 of this prospectus supplement and under the caption Risk Factors in our Annual Report on Form 10-K for the year ended December 31, 2014 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 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 two lead programs address significant unmet medical needs in the area of thrombosis, or blood clots. Our first lead compound Betrixaban is a novel oral once-daily inhibitor of Factor Xa in Phase 3 clinical trials 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 lead compound Andexanet alfa, an FDA-designated breakthrough therapy, is a recombinant protein designed to reverse anticoagulant activity in patients treated with a Factor Xa inhibitor. Andexanet alfa has potential indications to treat patients who are taking a direct or indirect Factor Xa inhibitor and who suffer a major bleeding episode or require emergency surgery. We are currently evaluating Andexanet alfa in Phase 3 clinical trials and a Phase 4 confirmatory trial. 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 interim Phase 1 data, we are advancing Cerdulatinib to the Phase 2a portion of the study which includes expansion cohorts.

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, using a hospital-based sales team in the United States and possibly other major markets and with partners in other territories.

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We currently have the following product candidates in development:

Development pipeline				
Product	**Description**	**Stage**	**Indication**	**Worldwide commercial rights**
Betrixaban	Oral Factor Xa inhibitor	Phase 3	Extended duration VTE prophylaxis in acute medically ill patients in-hospital and post discharge for 35 days	Portola
Andexanet alfa	Antidote for Factor Xa inhibitors	Phase 3 and Phase 4	Reversal of Factor Xa inhibitor anticoagulation	Portola
Cerdulatinib	Oral Dual Syk and JAK inhibitor	Phase 1/2a	B-cell hematologic cancers	Portola
Syk-selective inhibitors	Syk inhibitor	Pre-clinical	Allergic asthma and other inflammatory disorders	Biogen Idec

Betrixaban

Betrixaban is a novel oral once-daily inhibitor of Factor Xa in development for extended duration VTE prophylaxis in acute medically ill patients for 35 days of in-hospital and post-discharge use. Acute medically ill patients are those who are hospitalized for serious non-surgical conditions, such as heart failure, stroke, infection, rheumatic disorders and pulmonary disorders. We estimate that in the G7 countries in 2014 there were 22.5 million acute medically ill patients for whom VTE prophylaxis was recommended by medical treatment guidelines. The current standard of care for VTE prophylaxis in this population is enoxaparin, an injectable low molecular weight heparin that is approved for a usual administration period of 6 to 11 days and up to 14 days and is not approved for use outside of the hospital. According to IMS Health Incorporated, or IMS, a healthcare industry information provider, worldwide sales of enoxaparin for the twelve months through March 2014 were in excess of $4.1 billion. We believe that use of enoxaparin in acute medically ill patients accounted for at least $2.0 billion of these sales.

Multiple large, global trials have demonstrated that there is substantial risk of VTE in acute medically ill patients with restricted mobility and other risk factors beyond the standard course of enoxaparin. Our Phase 3 APEX study is designed to use biomarkers to identify and enroll patients most likely to benefit from therapy with Betrixaban. Specifically, these patients have elevated blood levels of D-dimer or are over age 75. There have been numerous publications highlighting the role of these two prognostic markers in identifying patients at extended risk of VTE. The MAGELLAN trial sponsored by Bayer Pharma AG, or Bayer, and Janssen Pharmaceuticals, Inc., or Janssen, which evaluated administration of rivaroxaban for an extended period, demonstrated that the incidence of VTE-related death rose four-fold over several weeks after hospital discharge and the discontinuation of treatment. However, there are no therapies approved for use beyond a typical hospitalization period of 6 to 14 days despite the ongoing risk of VTE faced by these patients for 35 days or more following hospital admission. We are developing Betrixaban to be the first oral Factor Xa inhibitor approved for use in acute medically ill patients and the first anticoagulant approved for hospital-to-home VTE prophylaxis in these patients. We believe the addressable market opportunity for Betrixaban could be $3.0 billion to $4.0 billion by 2020.

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In 2012, we initiated our pivotal biomarker-based Phase 3 APEX study, a randomized, double-blind, active-controlled, multicenter, multinational study to evaluate a once-daily dose of Betrixaban for 35 days for superiority as compared to in-hospital administration of enoxaparin once daily for 6 to 14 days followed by placebo. Our APEX study is over 70% enrolled in 35 countries worldwide. We believe Betrixaban has the potential to succeed in this patient population, in part due to its validated mechanism of action, but most importantly, due to its properties that differentiate it from other anticoagulants. First, it has the longest half-life, making it a true, once-daily therapy allowing for a narrow peak-to-trough concentration ratio that helps maintain a less variable anticoagulant effect over the course of a day. Second, it has the lowest renal clearance of all of the Factor Xa inhibitors, which may result in a lower rate of bleeding. And finally, it is not metabolized in the liver by an enzyme called CYP 3A4, which may result in reduced potential for drug-on-drug interactions. These properties are critically important for acute medically ill patients who are often renally compromised and on multiple concomitant medications.

In February 2015, the Independent Data Monitoring Committee, or IDMC, recommended that the Phase 3 APEX study of Betrixaban continue as planned without modification based on the successful completion of a pre-specified futility analysis. In making this recommendation, the IDMC evaluated preliminary efficacy trends and safety reports from the first 50% of the patients enrolled.

Andexanet alfa

Andexanet alfa, an FDA-designated breakthrough therapy, is a recombinant protein designed to reverse the anticoagulant activity in patients treated with a Factor Xa inhibitor. Andexanet alfa has potential indications to treat patients who are taking a direct or indirect Factor Xa inhibitor and who suffer a major bleeding episode or require emergency surgery. Currently, there is no antidote or reversal agent approved for use against Factor Xa inhibitors. Leading clinicians have identified, and the United States Food and Drug Administration, or FDA, has recognized, the lack of an effective reversal agent for Factor Xa inhibitors as a significant unmet clinical need. Based on industry data, we estimate that in 2020, between 23 million and 36 million patients will be treated with Factor Xa inhibitors, including low molecular weight heparins, for short-term use or chronic conditions. Clinical trial results suggest that, depending on their underlying medical condition, annually between 1% and 4% of these patients may experience a major bleeding event and an additional 1% may require emergency surgery. We believe that Andexanet alfa, if approved, has the long-term potential to address a total worldwide market in excess of $2.0 billion.

Andexanet alfa is the first therapy to demonstrate reversal of the anticoagulant activity of Factor Xa inhibitors as measured by anti-Factor Xa levels. We have initiated two Phase 3 ANNEXA™ (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) studies one with Bristol-Myers Squibb Company, or BMS, and Pfizer Inc. s, or Pfizer s, Factor Xa inhibitor, apixaban and one with Bayer Pharma AG, or Bayer, and Janssen Pharmaceuticals, Inc. s, or Janssen s, Factor Xa inhibitor, rivaroxaban. Our Phase 3 studies each consist of two parts. In the first part of each study, the effect of a single bolus of Andexanet alfa was evaluated in healthy volunteers who had been given apixaban or rivaroxaban. In the second part of each study, the ability of Andexanet alfa to sustain reversal of the anticoagulant effects of apixaban and rivaroxaban will be evaluated by administering a bolus plus infusion of Andexanet alfa to healthy volunteers who have been given apixaban or rivaroxaban. The first part of our Phase 3 ANNEXA™ studies of a single bolus of Andexanet alfa with apixaban and with rivaroxaban both met their primary and secondary endpoints with high statistical significance (p-values of less than 0.0001). The second part of our Phase 3 ANNEXA™ studies is ongoing with results expected in the first half of 2015. In early 2015, we initiated a Phase 4 ANNEXA™ confirmatory patient study, as agreed to by the FDA and EMA as part of an accelerated approval pathway for Andexanet alfa. This open-label, single-arm study is being conducted in patients receiving apixaban, rivaroxaban or enoxaparin (a low molecular weight heparin) who present with an acute major bleed. Pursuant to discussions with the FDA, we plan to include data from a small number of patients from this study in our Biologics License Application, or BLA, which we expect to submit in 2015 for conditional approval.

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We completed a series of Phase 2 proof-of-concept studies evaluating the safety and activity of Andexanet alfa in healthy volunteers who were administered one of several Factor Xa inhibitors. Analysis of anticoagulation markers in blood samples taken from the subjects in these studies demonstrated that Andexanet alfa produced immediate reversal of anticoagulant activity of the Factor Xa inhibitors apixaban, rivaroxaban and enoxaparin and that the reversal could be sustained. Additionally, we are conducting a Phase 2 proof-of-concept study evaluating the reversal of edoxaban and we plan to initiate a Phase 2 study evaluating the reversal of Betrixaban.

We have entered into collaboration agreements with BMS and Pfizer, with Bayer and Janssen and with Daiichi Sankyo, Inc., or Daiichi Sankyo, to support Phase 2 and Phase 3 clinical studies with apixaban, rivaroxaban and edoxaban, respectively. Collectively, these clinical collaborations represent over $100 million in upfront, contingent and potential milestone payments to Portola. We retain full commercial rights with respect to Andexanet alfa.

Cerdulatinib

Cerdulatinib is an orally available, potent dual spleen tyrosine kinase (Syk) and janus kinase (JAK) inhibitor. Scientists have demonstrated that both Syk and JAK play key roles in various hematologic cancers and inflammatory diseases. We are developing Cerdulatinib for treatment of certain B-cell hematologic cancers, with a particular focus on patients who have NFkB activating mutations or acquired mutations to other novel B-cell targeted therapies that cause treatment failure or disease relapse. Cerdulatinib has completed preclinical testing and has demonstrated in-vitro activity in cancer cell lines with NFkB activating mutations and in patient tumor samples with acquired mutations to novel B-cell targeted drug candidates. In October 2013, we initiated a Phase 1/2a proof-of-concept study in NHL, and CLL, patients. In the Phase 1 dose escalation portion of the study, we have yet to reach the maximum tolerated dose and enrollment continues. We presented interim Phase 1 data at the American Society of Hematology meeting in December 2014, and as a result we are advancing Cerdulatinib into the Phase 2a portion of the study which includes expansion cohorts at the recommended Phase 2 dose.

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:

- Successfully complete the clinical development of Betrixaban;
- Advance Andexanet alfa through an expedited development and approval process;
- Commercialize Betrixaban and Andexanet alfa, if approved, in the United States using a hospital-focused sales force;
- Advance Cerdulatinib for treatment of hematologic cancers; and
- Deploy capital strategically to develop 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 with Biogen Idec, Merck and Novartis Pharma A.G., and our agreements with BMS and Pfizer and Daiichi Sankyo. We have not generated any commercial product revenue. Our operating expenses increased during 2014 and we expect that they will continue to increase in 2015 and beyond as we accelerate our efforts to obtain regulatory approval and support the planned commercialization of our oral Factor Xa inhibitor,

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Betrixaban, and our Factor Xa inhibitor antidote, Andexanet alfa and the advance of Cerdulatinib. As of December 31, 2014, we had $392.3 million of cash, cash equivalents and investments.

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 and in our Annual Report on Form 10-K for the year ended December 31, 2014 filed with the Securities Exchange Commission on March 2, 2015, including the following:

- We do not have any products approved for sale and expect to incur substantial and increasing losses for the foreseeable future;
- Our operating results may fluctuate significantly, are difficult to predict and could fall below expectations;
- We will need additional funds to support our operations, and such funding may not be available on acceptable terms or at all;
- Our success depends heavily on the approval and successful commercialization of our lead product candidates, Betrixaban and Andexanet alfa;
- Clinical studies of our product candidates will be 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, we may need to abandon our development or commercialization of that product candidate;
- Our APEX study of Betrixaban may fail due to a potential risk of increased bleeding or lack of efficacy, as experienced in two of our competitors clinical trials evaluating Factor Xa inhibitors for VTE prophylaxis in acute medically ill patients;
- If Betrixaban, Andexanet alfa or any of our other product candidates is approved for sale, we will be allowed to market it only for the specific indication for which it receives approval, which 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.

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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) 246-7300. 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.

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The offering

Common stock offered by us	2,495,652 shares
Common stock to be outstanding immediately after this offering	51,262,458 shares
Underwriter s option	The underwriter has an option to purchase up to 374,348 additional shares of common stock from us as described in Underwriting.
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 underwriter exercises its 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. We intend to use all of the net proceeds from this offering, along with our other capital resources, to fund pre-launch commercial manufacturing and infrastructure costs for Andexanet alfa and Betrixaban in addition to our ongoing Phase 3 study of Betrixaban, clinical and manufacturing work to support our Biologics License Application for Andexanet alfa and our Phase 1/2a proof-of-concept study of Cerdulatinib in hematologic cancers, and for working capital, capital expenditures and other general corporate purposes, which may include the acquisition or licensing of other products, businesses or technologies. See Use of proceeds for additional information.
Risk factors	See Risk factors beginning on page S-8 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

The number of shares of our common stock to be outstanding after this offering is 51,262,458, based on 48,766,895 shares of our common stock outstanding as of December 31, 2014, and excludes the following:

- 4,249,168 shares of our common stock issuable upon the exercise of stock options outstanding as of December 31, 2014, at a weighted-average exercise price of $9.67 per share;

934,205 shares of our common stock reserved for future issuance under our 2013 Equity Incentive Plan;

1,789,577 shares of our common stock reserved for future issuance under our 2013 Employee Stock Purchase Plan; and

6,240 shares of our common stock issuable upon the exercise of common stock warrants outstanding at a weighted-average exercise price of $10.75 per share.

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

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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 and the information set forth under the caption Risk Factors in our Annual Report on Form 10-K for the year ended December 31, 2014, 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.

Risks related to this offering and ownership of our common stock

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

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

- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- 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 and the information set forth under the caption Risk Factors in our Annual Report on Form 10-K for the year ended December 31, 2014.

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. 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.

Our executive officers, directors and principal stockholders have the ability to significantly influence all matters submitted to stockholders for approval.

Based, in part, on a review of SEC filings, we believe that our executive officers, directors and stockholders who own more than 5% of our outstanding common stock beneficially own close to half of our outstanding shares of common stock, based on shares of common stock outstanding as of December 31, 2014. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders, if they choose to act together, will significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

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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 forecast of analysts, our stock price will likely decline.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the balance of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

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

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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 employment 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.

Certain of our executive officers are parties to employment agreements that contain change in control and severance provisions providing for aggregate cash payments of up to approximately $2.4 million for severance and other benefits and acceleration of vesting of stock options with a value of approximately $39.3 million as of December 31, 2014, based on the closing price of our common stock of $28.32 on such date in the event of a termination of employment in connection with a change in control of us. The accelerated vesting of options 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.

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.

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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 ability to enroll patients in our clinical studies at the pace that we project;
- our ability to scale up manufacturing of our product candidates to commercial scale;
- the timing and the success of the design of our Phase 3 clinical study of Betrixaban, or APEX; the timing and the success of our Phase 3 registration study and Phase 4 confirmatory study of Andexanet alfa;
- the timing and the success of our anticipated additional Phase 2 proof-of-concept studies of Andexanet alfa;
- potential indications for Andexanet alfa;
- our ability to submit a Biologics License Application, or BLA, for 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;
- our ability to conduct a proof-of-concept study in hematologic cancers for Cerdulatinib;
- our expectation that our existing capital resources and the net proceeds from this offering will be sufficient to enable us to complete our ongoing Phase 3 clinical study of Betrixaban, advance our clinical development

of Andexanet alfa, including related manufacturing and a Biologics License Application and our Phase 1/2a proof-of-concept studies of Cerdulatinib in hematologic cancers;

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

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

our ability to compete with branded and generic Factor Xa inhibitors;

our reliance on third parties to conduct our clinical studies;

our reliance on third-party contract manufacturers to manufacture and supply 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;

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- 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, in any free writing prospectuses we may authorize for use in connection with this offering, and in our annual report on Form 10-K for the year ended December 31, 2014 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.

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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 underwriter exercises its option in full, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of December 31, 2014, we had cash, cash equivalents and investments of $392.3 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 advance Betrixaban, including completing enrollment of our Phase 3 APEX study, submission of our New Drug Application and pre-launch commercial manufacturing and infrastructure needs;

- approximately $225 million to advance Andexanet alfa, including clinical and manufacturing work to support submitting our Biologics License Application, and pre-launch commercial manufacturing and infrastructure needs; and

- the balance to fund Cerdulatinib Phase 1/2a study, including expansion cohorts, working capital, capital expenditures and other general corporate purposes, which may include the acquisition or licensing of other products, businesses or technologies.

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: enable us to complete our ongoing Phase 3 clinical study of Betrixaban, our Phase 2 proof-of-concept studies and expansion cohorts and Phase 3 registration study (assuming an expedited approval process) of Andexanet alfa, our Phase 1/2 proof-of-concept study in non-Hodgkin s lymphoma and chronic lymphocytic leukemia for Cerdulatinib; to continue our Phase 4 confirmatory study for Andexanet alfa; and to support pre-launch manufacturing and commercial infrastructure needs for Andexanet alfa and Betrixaban. 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.

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.

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

The following is a summary of the material United States federal income and estate 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 and estate tax consequences relating thereto, does not address the potential application of the Medicare contribution tax and does not address any gift 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 and estate 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, 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, 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 AND ESTATE 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

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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.

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Gain on disposition of our common stock

Subject to the discussion regarding backup withholding and FATCA (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.

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.

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

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.

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. Notwithstanding the foregoing, backup withholding may apply if the payor has actual knowledge, or reason to know, that the non-U.S. holder is a United States person who is not an exempt recipient.

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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, 2016.

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

Estate tax

Individual non-U.S. holders and entities whose property is potentially includible in such an individual s gross estate for United States federal estate tax purposes (for example, a trust funded by such an individual and with respect to which the individual has retained certain interests or powers), should note that, absent an applicable treaty benefit, our common stock generally will be treated as United States situs property subject to United States federal estate tax.

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Underwriting

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriter, Morgan Stanley & Co. LLC, has agreed to purchase, and we have agreed to sell to it the number of shares indicated below:

Name	Number of shares
Morgan Stanley & Co. LLC	
Total:	2,495,652

The underwriter is offering the shares of common stock subject to its acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the underwriter 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 underwriter is 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 underwriter is not required to take or pay for the shares covered by the underwriter s option to purchase additional shares described below.

The underwriter initially proposes 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 underwriter.

We have granted to the underwriter an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 374,348 additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions.

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 underwriter s 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 $. We have agreed to reimburse the underwriter for expenses of up to $ relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc. The underwriter has agreed to make

certain reimbursements to us in connection with this offering.

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

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We, our directors and our executive officers have agreed that with the exception of 153,000 shares that may be sold pursuant to 10b5-1 trading plans, 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 Securities and Exchange Commission 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 underwriter; 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 underwriter and (ii) no filing under Section 16(a) of the Exchange Act shall be required or voluntarily made during the restricted period;

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

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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 underwriter may engage in transactions that stabilize, maintain or otherwise affect the price of our common stock. Specifically, the underwriter may sell more shares than it is 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 underwriter under the option. The underwriter 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 underwriter will consider, among other things, the open market price of shares compared to the price available under the option. The underwriter may also sell shares in excess of the option, creating a naked short position. The underwriter 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 underwriter is 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 underwriter may bid for, and purchase, shares of common stock on The Nasdaq Global Select Market to stabilize the price of our common stock. 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 underwriter is not required to engage in these activities and may end any of these activities at any time. Neither we nor the underwriter makes 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 the underwriter makes any representation that the underwriter will engage in these stabilizing transactions or that any transaction, once commenced, will not be discontinued without notice.

We and the underwriter 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 the underwriter in this offering. The underwriter may allocate a number of shares of common stock for sale to its online brokerage account holders. Internet distributions will be allocated on the same basis as other allocations.

The underwriter and its affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging. financing and brokerage activities. The underwriter and its 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 underwriter and its 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

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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. The underwriter and its 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 underwriter has represented and agreed that:

(a) it has 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 Section 21 of the Financial Services and Markets Act 2000 (FSMA) received by it 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) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

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Legal matters

Cooley LLP, San Francisco and Palo Alto, California, will pass upon the validity of the shares of common stock offered hereby. The underwriter is being represented by Davis Polk & Wardwell LLP, Menlo Park, California, in connection with the offering.

Experts

The consolidated financial statements of Portola Pharmaceuticals, Inc. appearing in Portola Pharmaceuticals, Inc. s Annual Report (Form 10-K) for the year ended December 31, 2014, and the effectiveness of Portola Pharmaceuticals, Inc. s internal control over financial reporting as of December 31, 2014 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such reports given on the authority of such firm 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 Securities and Exchange Commission, or 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, 2014, which was filed with the SEC on March 2, 2015;
- our Current Reports on Form 8-K filed with the SEC on January 26, 2015, February 2, 2015 and February 10, 2015;
- 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; and

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 4, 2014.

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 Securities Exchange Act of 1934, as amended, or the

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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) 246-7300

Attn: Secretary

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Prospectus

Up to 10,000,000 Shares of Common Stock

From time to time, we may offer and sell shares of common stock in amounts, at prices and on terms described in one or more supplements to this prospectus.

This prospectus describes some of the general terms that may apply to an offering of our common stock. 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.

We may offer and sell shares of common stock to or through one or more underwriters, dealers and agents, or directly to purchasers, 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 options for additional shares 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.

Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. On September 30, 2014, the last reported sale price of our common stock was $25.28 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 common stock 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.

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 October 1, 2014.

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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, in one or more offerings, shares of our common stock as described in this prospectus. This prospectus provides you with a general description of the shares we may offer.

Each time we offer shares of our common stock 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 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.

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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.

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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 two lead programs address significant unmet medical needs in the area of thrombosis, or blood clots. Our lead compound Betrixaban is a novel oral once-daily inhibitor of Factor Xa in Phase 3 development for extended duration prophylaxis, or preventive treatment, of a form of thrombosis known as venous thromboembolism, or VTE, in acute medically ill patients for up to 35 days of in-hospital and post-discharge use. Currently, there is no anticoagulant approved for extended duration VTE prophylaxis in this population. Our second lead development candidate Andexanet alfa, an FDA-designated breakthrough therapy is a recombinant protein designed to reverse the anticoagulant activity in patients treated with a Factor Xa inhibitor who suffer an uncontrolled bleeding episode or undergo emergency surgery. Andexanet alfa is currently being evaluated in Phase 3 clinical trials. Our third product candidate, Cerdulatinib, formerly PRT2070, is an orally available kinase inhibitor that inhibits spleen tyrosine kinase, or Syk, and janus kinases, or JAK, enzymes that regulate important signaling pathways and is being developed for hematologic, or blood, cancers and inflammatory disorders. We are currently in a Phase 1/2 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. Our fourth program of highly selective Syk inhibitors is partnered with Biogen Idec Inc.

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.

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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) 246-7300. 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.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012. As such, we are eligible for exemptions from various reporting requirements applicable to other public companies that are not emerging growth companies, including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002 and reduced disclosure obligations regarding executive compensation. We will remain an emerging growth company until December 31, 2014, at which time we will become a large accelerated filer.

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 expenses and capital expenditures. See Use of Proceeds in this prospectus.

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.

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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:

- our ability to enroll patients in our clinical studies at the pace that we project;
- our ability to scale up manufacturing of our product candidates to commercial scale;
- the timing and the success of the design of our Phase 3 clinical study of Betrixaban, or APEX;
- the timing of our anticipated Phase 3 registration study and Phase 4 confirmatory study of Andexanet alfa;
- the timing of our anticipated additional Phase 2 proof-of-concept studies 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;

our expectation that our existing capital resources and the net proceeds from this offering will be sufficient to enable us to complete our ongoing Phase 3 clinical study of Betrixaban, initiate our Phase 3/4 Biologics License Application enabling studies and related manufacturing of Andexanet alfa and our Phase 1/2 proof-of-concept studies of Cerdulatinib in hematologic cancers;

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

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

our ability to compete with branded and generic Factor Xa inhibitors;

our reliance on third parties to conduct our clinical studies;

our reliance on third-party contract manufacturers to manufacture and supply 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.

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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 expenses and 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.

DESCRIPTION OF CAPITAL STOCK

General

As of June 30, 2014, 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.

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.

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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 June 30, 2014, 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.

As of June 30, 2014, we had a warrant to purchase the number of shares of our common stock equal to 1.9% of our utilization of the credit line provided by General Electric Capital Corporation, rounded down to the nearest whole share, with an exercise price of $10.00 per share outstanding. As of June 30, 2014, there were 4,740 shares of our common stock issuable pursuant to the exercise of this warrant. This warrant 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 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, this warrant will expire on January 21, 2015.

As of June 30, 2014, we had a warrant to purchase 7,633 shares of our common stock with an exercise price of $13.10 per share outstanding. This warrant 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, this warrant will expire on September 29, 2016.

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,

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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;

- 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.

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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.

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.

Transfer agent and registrar

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

PLAN OF DISTRIBUTION

We may offer and sell shares of our common stock in offerings hereunder to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis. We will provide the specific plan of distribution for any shares of our common stock to be offered by us in a supplement to this prospectus.

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 financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2013, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP s report, given on their authority as experts in accounting and auditing.

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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, 2013, which was filed with the SEC on March 3, 2014 (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 4, 2014;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2014, which was filed with the SEC on May 13, 2014;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2014, which was filed with the SEC on August 6, 2014;
- our Current Reports on Form 8-K filed with the SEC on March 18, 2014, March 19, 2014, April 2, 2014, May 16, 2014, May 27, 2014, July 2, 2014 (two filings) and October 1, 2014; 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) 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.

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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: Secretary

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