

PORTOLA PHARMACEUTICALS INC
Form 424B5
December 03, 2015
Table of Contents

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

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

Subject to completion, dated December 3, 2015

Preliminary Prospectus Supplement to Prospectus dated November 9, 2015

2,600,000 Shares

Portola Pharmaceuticals, Inc.

Common Stock

We are offering 2,600,000 shares of our common stock. Our common stock is listed on The NASDAQ Global Select Market under the trading symbol PTLA. On December 2, 2015, the last reported sale price of our common stock on The NASDAQ Global Select Market was \$51.05 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 underwriters sell more than 2,600,000 shares of common stock, the underwriters have an option to purchase 390,000 additional shares of common stock from us at the public offering price, after deducting underwriting discounts and commissions.

The underwriters expect to deliver the shares against payment in New York, New York on December , 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

Credit Suisse

Citigroup

Cowen and Company

Prospectus supplement dated December , 2015

Table of Contents

Table of contents

Prospectus supplement

	Page
<u>About this prospectus supplement</u>	S-ii
<u>Prospectus supplement summary</u>	S-1
<u>Risk factors</u>	S-8
<u>Special note regarding forward-looking statements</u>	S-11
<u>Use of proceeds</u>	S-13
<u>Dividend policy</u>	S-14
<u>Material United States federal income and estate tax consequences to non-U.S. holders</u>	S-15
<u>Underwriting</u>	S-19
<u>Legal matters</u>	S-24
<u>Experts</u>	S-24
<u>Where you can find more information</u>	S-24
<u>Incorporation of certain information by reference</u>	S-24

Prospectus

	Page
<u>About This Prospectus</u>	i
<u>Prospectus Summary</u>	1
<u>Risk Factors</u>	6
<u>Special Note Regarding Forward-Looking Statements</u>	6
<u>Use of Proceeds</u>	8
<u>Ratio of Earnings to Fixed Charges</u>	8
<u>Description of Capital Stock</u>	8
<u>Description of Debt Securities</u>	11
<u>Description of Warrants</u>	18
<u>Legal Ownership of Securities</u>	20
<u>Plan of Distribution</u>	23
<u>Legal Matters</u>	25
<u>Experts</u>	25
<u>Where You Can Find More Information</u>	25
<u>Incorporation of Certain Information by Reference</u>	25

Table of Contents

About this prospectus supplement

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

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

Where you can find more information in this prospectus supplement and in the accompanying prospectus, before investing in our common stock.

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

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

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

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

S-ii

Table of Contents

Prospectus supplement summary

*This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus, and does not contain all of the information that you need to consider in making your investment decision. This prospectus supplement and the accompanying prospectus include information about the shares of common stock that we are offering as well as information regarding our business. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety. You should carefully consider the information set forth under **Risk factors** beginning on page S-8 of this prospectus supplement and under the caption **Risk Factors** in our *Quarterly Report on Form 10-Q* for the quarterly period ended September 30, 2015 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.

Our Phase 3 programs address significant unmet medical needs in the area of thrombosis, or blood clots. Betrixaban, a Food and Drug Administration, or FDA,-designated Fast-Track novel oral once-daily inhibitor of Factor Xa, is in a Phase 3 clinical trial for extended duration prophylaxis, or preventive treatment, of a form of thrombosis known as venous thromboembolism, or VTE, in acute medically ill patients for 35 days of in-hospital and post-discharge use. Currently, there is no anticoagulant approved for extended duration VTE prophylaxis in the acute medically ill population. Our second Phase 3 compound, Andexanet alfa, an FDA-designated breakthrough therapy and orphan drug, is a recombinant protein designed to reverse anticoagulant activity in patients treated with a Factor Xa inhibitor. Andexanet alfa has potential indications to reverse anticoagulant activity in patients who are taking a direct or indirect Factor Xa inhibitor and who suffer a major bleeding episode or require emergency surgery. We have completed the Phase 3 registration studies of Andexanet alfa and are currently evaluating it in Phase 2 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. We are exploring alternate dosing regimens and formulations to get a higher exposure of Cerdulatinib in patients. Based on interim Phase 1 data, we plan to advance Cerdulatinib to the Phase 2a portion of the study, which includes expansion cohorts in select hematologic cancers. We also have a program of highly selective Syk inhibitors, one of which is partnered with Ora, Inc., or Ora.

Our product candidates and collaboration agreements

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. 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

S-1

Table of Contents

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 enrollment is complete and on track for blinded, pooled event rates and quality metrics in 35 countries worldwide.

We believe Betrixaban has the potential to succeed in the targeted patient population, in part due to its validated mechanism of action, but also most importantly, due to its properties that differentiate it from other anticoagulants. First, it has the longest half-life of all the Factor Xa inhibitors, 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 the Factor Xa inhibitors, which may result in a lower rate of bleeding. 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 the third quarter of 2015, we completed a planned protocol-defined sample size re-assessment and increased the size of the trial from 6,850 to approximately 7,500 patients. The increase in sample size ensures APEX statistical power for the primary efficacy analysis patient cohort and increases power in the overall patient population analysis. We finalized our statistical analysis plan in agreement with the FDA. We completed APEX patient enrollment in the fourth quarter of 2015 and expect to report top line data in the first quarter of 2016, and we expect to submit a new drug application, or NDA, to the FDA in the third quarter of 2016. In the fourth quarter of 2015, Betrixaban received Fast-Track designation from the FDA for prevention of blood clots in acute medically ill patients. Fast-Track designation is generally intended by the FDA to facilitate the development, and expedite the review, of drugs which treat a serious or life-threatening condition and fill an unmet medical need.

In early 2013, we entered into a clinical collaboration agreement with Lee's Pharmaceutical (HK) Ltd, or Lee's, to jointly expand the Phase 3 APEX study of Betrixaban into China with an exclusive option for Lee's to negotiate for the exclusive commercial rights to Betrixaban in China.

Andexanet alfa

Andexanet alfa, an FDA-designated breakthrough therapy and orphan drug, is a recombinant protein designed to reverse anticoagulant activity in patients treated with a Factor Xa inhibitor. Andexanet alfa has potential indications to reverse anticoagulant activity in patients who are taking a direct or indirect Factor Xa inhibitor and who suffer a major bleeding episode or who require emergency surgery. Currently, there is no antidote or reversal agent approved for use against Factor Xa inhibitors. 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 completed two Phase 3 ANNEXA™ (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) studies – one with the Bristol-Myers Squibb Company, or BMS, and Pfizer Inc., or Pfizer, Factor Xa inhibitor, apixaban, and one with the Bayer Pharma AG, or Bayer, and Janssen Pharmaceuticals, Inc., or Janssen, Factor Xa inhibitor, rivaroxaban. Our Phase 3 studies each consisted 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 was evaluated by administering a bolus plus infusion of Andexanet alfa to healthy volunteers who had 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 of a bolus plus infusion of Andexanet alfa with apixaban and with rivaroxaban both also met their primary and secondary endpoints with high statistical significance (p-value of less than 0.0001). In early 2015, we initiated a Phase 4 ANNEXA™ confirmatory patient study, as agreed to by the FDA and European Medicines Agency, or EMA. This study is part of an accelerated approval pathway in the United States for Andexanet alfa. This open-label, single-arm study is being conducted in patients receiving apixaban,

rivaroxaban, edoxaban or enoxaparin (a low molecular weight heparin) who present with certain types of acute major bleeds. Pursuant to active and ongoing discussions with the FDA, we plan to include data from the initial

S-2

Table of Contents

patients enrolled in this study in our Biologics License Application, or BLA. We have initiated a rolling submission of the BLA to the FDA and expect the BLA submission to be completed by the end of 2015.

We have also 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 include data from this study in our BLA. We have also initiated a Phase 2 proof-of-concept study evaluating Andexanet alfa for the reversal of the anticoagulant activity of Betrixaban.

Our current Phase 2 and Phase 4 ANNEXA™ studies are using clinical material from CMC Biologics, Inc., or CMC Biologics. We are currently continuing and expanding our ongoing work with CMC Biologics from clinical supply to commercial supply for our BLA filing and potential U.S. launch. Under our commercial supply agreement, CMC Biologics plans to increase production capacity at a lower cost than that of our current clinical supply for Andexanet alfa. We are also working with Lonza Group Ltd., or Lonza, to develop a large-scale manufacturing process. Under our manufacturing supply agreement with Lonza, we plan to further increase our production capacity and to enhance our manufacturing process at Lonza to provide broader worldwide supply following our potential U.S. launch.

In January 2014, we entered into a collaboration agreement with BMS and Pfizer to further study Andexanet alfa as a reversal agent for their jointly owned FDA-approved oral Factor Xa inhibitor, apixaban, through Phase 3 studies. We initiated Phase 3 studies in the first quarter of 2014. Under the terms of the agreement, we received an upfront payment of \$13.0 million, subject to a 50% refund provision, and are eligible to receive additional development and regulatory milestone and contingent payments of up to \$12.0 million, subject to a 50% refund provision. These payments represent the total consideration under this agreement. BMS and Pfizer will continue to provide development and regulatory guidance for the program. Under this agreement with BMS and Pfizer, we retain full worldwide development and commercial rights to Andexanet alfa. This Phase 3 collaboration agreement will continue in force until the approval of Andexanet alfa as a reversal agent for apixaban by the FDA and EMA. BMS and Pfizer may terminate this agreement for convenience with 60 days advance written notice or for our bankruptcy or change of control. In addition, either party may terminate this agreement for the other party's uncured material breach, material safety issues or failure of the Phase 3 studies.

In February 2014, we entered into a second collaboration agreement with Bayer and Janssen to evaluate Andexanet alfa as a reversal agent for the FDA-approved oral Factor Xa inhibitor, rivaroxaban, through Phase 3 studies. Our initial collaboration agreement with Bayer and Janssen covers the conduct of a Phase 2 proof-of-concept study. The new collaboration agreement covers the conduct of Phase 3 studies of Andexanet alfa with rivaroxaban and any potential U.S. and European Union regulatory approval of Andexanet alfa as a reversal agent of rivaroxaban. Under this collaboration agreement, we received an upfront payment of \$10.0 million and are eligible to receive additional development and regulatory milestone payments of up to \$15.0 million. These payments represent the total consideration under this agreement. Bayer and Janssen will continue to provide development and regulatory guidance for the program.

Under both agreements with Bayer and Janssen, we retain full worldwide development and commercial rights to Andexanet alfa. This Phase 3 collaboration agreement will continue in force until the approval of Andexanet alfa as a reversal agent for rivaroxaban by the FDA and EMA. Bayer and Janssen may terminate this agreement for convenience with 60 days advance written notice or for our bankruptcy or change of control. In addition, either party may terminate this agreement for the other party's uncured material breach or material safety issues, or we can also terminate this agreement for failure of the Phase 3 studies.

S-3

Table of Contents

In July 2014, we entered into a collaboration agreement with Daiichi Sankyo to include subjects dosed with edoxaban, its Factor Xa inhibitor product, in one of our Phase 3 studies of Andexanet alfa. We are responsible for the cost of conducting this clinical study. Daiichi Sankyo will work closely with us on both development and regulatory aspects of Andexanet alfa in connection with our Phase 3 study to the extent such matters relate to edoxaban. Pursuant to our agreement with Daiichi Sankyo, we are obligated to provide research and development and regulatory approval services and participate on various committees. Under this collaboration agreement, we received an upfront payment of \$15.0 million in the third quarter of 2014 and are eligible to receive additional payments of up to \$25.0 million, due upon the achievement of certain milestones associated with the progress of our Phase 3 study.

Cerdulatinib

In addition to our thrombosis products, we are developing orally available kinase inhibitors to treat hematologic disorders and inflammation. Cerdulatinib is an orally available, potent inhibitor of syk and JAK, enzymes that regulate two important signaling pathways. We are developing Cerdulatinib for the treatment of certain B-cell hematologic cancers. We are currently in a Phase 1/2a proof-of-concept study with Cerdulatinib in NHL and CLL. In the Phase 1 dose escalation portion of the study, we have yet to reach the maximum tolerated dose, and enrollment continues. We are exploring alternate dosing regimens and formulations to get a higher exposure. Based on interim Phase 1 data, we plan to advance Cerdulatinib to the Phase 2a portion of the study, which includes expansion cohorts in select hematologic cancers.

Selective Syk Inhibitors

Syk is an important mediator of immune response in a number of different types of immune cells. Our selective Syk inhibitors have been successfully evaluated in 131 subjects in several Phase 1 clinical studies. Ora is leading the pre-clinical study of a selective Syk inhibitor for ophthalmic diseases.

In May 2015, we entered into a license and collaboration agreement with Ora pursuant to which we granted Ora an exclusive license to co-develop and co-commercialize one of our specific Syk inhibitors, PRT02761. Ora has the primary responsibility for conducting the research and development and regulatory activities under this agreement. We are obligated to provide assistance in accordance with the agreed-upon development plan, as well as participate on various committees.

Under the terms of this risk and cost sharing agreement, each party will incur its own share of development costs. Third-party related development costs will be shared by Ora and us at approximately 60% and 40%, respectively, until an End of Phase 2 meeting with the FDA, and equally thereafter. We are entitled to receive either 50% of the profits, if any, generated by future sales of the products developed under the agreement or royalty payments on such sales, should we opt out of the agreement.

We may opt out of the agreement any time prior to 90 days after an End of Phase 2 meeting with the FDA. The timing of the exercise of our opt out rights would impact future royalties we would be entitled to receive from Ora. Each party may also buy out the rights and interests in the licensed compound by paying the greater of \$6.0 million or two times the actual aggregate development cost incurred by both parties on or before the date that is 90 days after an End of Phase 2 meeting with the FDA.

S-4

Table of Contents

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, 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 have increased during 2015, and we expect that they will continue to increase in 2016 and beyond as we accelerate our efforts to obtain regulatory approval and support the planned commercialization of our oral Factor Xa inhibitor, Betrixaban, and our Factor Xa inhibitor antidote, Andexanet alfa, and to advance the development of Cerdulatinib. As of September 30, 2015, we had \$356.0 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 Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2015 filed with the SEC on November 9, 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;

Table of Contents

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.

Company Information

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

Table of Contents

The offering

Common stock offered by us 2,600,000 shares

Common stock to be outstanding immediately after this offering 55,305,617 shares

Underwriters option The underwriters have an option to purchase up to 390,000 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 underwriters exercise their option in full, based on the assumed public offering price of \$ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering, along with our other capital resources, to fund our on-going clinical and pre-launch commercial activities for Andexanet alfa and Betrixaban in addition to our on-going clinical work for Cerdulatinib. Additionally, we will use the net proceeds for initial E.U. pre-commercial and regulatory activities for Andexanet alfa and Betrixaban, assessment of long-term strategic manufacturing options for Andexanet alfa and expansion of the ANNEXA-4 trial to include a surgical patient cohort and for new research activities. The remainder will be used 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 55,305,617, based on 52,705,617 shares of our common stock outstanding as of October 30, 2015, and excludes the following:

Edgar Filing: PORTOLA PHARMACEUTICALS INC - Form 424B5

5,007,043 shares of our common stock issuable under restricted stock units and upon the exercise of stock options outstanding as of October 30, 2015, at a weighted-average exercise price of \$23.77 per share;

1,580,298 shares of our common stock reserved for future issuance under our 2013 Equity Incentive Plan;

1,759,270 shares of our common stock reserved for future issuance under our 2013 Employee Stock Purchase Plan; and

1,500 shares of our common stock issuable upon the exercise of common stock warrants outstanding as of October 30, 2015, at a weighted-average exercise price of \$13.10 per share.

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

S-7

Table of Contents

Risk factors

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, together with all the other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus and the information set forth under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2015, before making an investment decision. The risks described below are not the only ones facing our company. Additional risks not presently known to us or that we currently deem immaterial may also impair our business operations. Our business, financial condition or results of operations could be materially and adversely affected by any of these risks. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks related to 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 experience 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.

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.

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

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

S-8

Table of Contents

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

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.

S-9

Table of Contents

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 \$2.5 million for severance and other benefits and acceleration of vesting of stock options with a value of approximately \$40.3 million as of September 30, 2015, based on the closing price of our common stock of \$42.62 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.

Table of Contents

Special note regarding forward-looking statements

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

our expected uses of the net proceeds to us from this offering;

anticipated timing of results from our Phase 3 clinical study of Betrixaban, or APEX;

our anticipated timing of our submission of a BLA and/or a NDA to the FDA;

our anticipated timing regarding possible commercial launch of our product candidates;

our commercial strategy for commercial launch of our product candidates;

the timing and the success of the design of APEX;

the timing of our Phase 2 proof-of-concept studies of Andexanet alfa;

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

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

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

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

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

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

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

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

our ability to successfully commercialize our products;

the rate and degree of market acceptance of our products;

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

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

our ability to compete with other commercial Factor Xa inhibitors;

our reliance on third parties to conduct our clinical studies;

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

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

our ability to retain and recruit key personnel;

Table of Contents

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

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

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

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

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

our financial performance; and

developments and projections relating to our competitors or our industry.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plan, anticipate, believe, estimate, project, predict, potential and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading Risk factors contained in this prospectus supplement and the accompanying prospectus, in any free writing prospectuses we may authorize for use in connection with this offering, and in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2015 as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus supplement and the accompanying prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus supplement, the accompanying prospectus, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Table of Contents

Use of proceeds

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

As of September 30, 2015, we had available cash, cash equivalents and investments of \$356.0 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 clinical and manufacturing work to support submitting our NDA, pre-launch commercial manufacturing and infrastructure needs in the U.S. and initial commercial activities assessing the opportunity to launch in the E.U.;

approximately \$300 million to advance Andexanet alfa, including clinical and manufacturing work to support submitting our BLA, an expansion of the ANNEXA-4 trial to include a surgical patient cohort, pre-launch commercial manufacturing and infrastructure needs in the U.S., strategic manufacturing initiatives to address long-term supply and initial commercial activities assessing the opportunity to launch in the E.U.; and

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

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

Based on our planned use of the net proceeds from this offering and our existing cash, cash equivalents and investments described above, we expect that such funds will be sufficient to: enable us to complete our ongoing Phase 3 clinical study of Betrixaban, our Phase 2 proof-of-concept studies and expansion cohorts 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 and commercial 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.

S-13

Table of Contents

Dividend policy

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

S-14

Table of Contents

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

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

This discussion is limited to non-U.S. holders who purchase our common stock issued pursuant to this offering and who hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all of the United States federal income tax consequences that may be relevant to a particular non-U.S. holder in light of such non-U.S. holder's particular circumstances. This discussion also does not consider any specific facts or circumstances that may be relevant to non-U.S. holders subject to special rules under the United States federal income tax laws, including, without limitation, certain former citizens or long-term residents of the United States, partnerships or other pass-through entities, 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

S-15

Table of Contents

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

Distributions on our common stock

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

Dividends (out of earnings and profits) paid to a non-U.S. holder of our common stock generally will be subject to United States federal withholding tax at a rate of 30% of the gross amount of the dividends, or such lower rate specified by an applicable income tax treaty, subject to the discussion below regarding FATCA. To receive the benefit of a reduced treaty rate, a non-U.S. holder must furnish to us or our paying agent a valid IRS Form W-8BEN or Form W-8BEN-E (or other applicable successor form) including a United States taxpayer identification number and certifying such non-U.S. holder's qualification for the reduced rate. This certification must be provided to us or our paying agent prior to the payment of dividends and must be updated periodically. If the non-U.S. holder holds the stock through a financial institution or other agent acting on the non-U.S. holder's behalf, the non-U.S. holder will be required to provide appropriate documentation to the agent, which then will be required to provide certification to us or our paying agent, either directly or through other intermediaries.

Non-U.S. holders that do not timely provide the required certification, but that qualify for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

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

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

Table of Contents

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; however, there can be no assurance that we will not become a USRPHC.

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

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.

S-17

Table of Contents

Backup withholding is not an additional tax. If any amount is withheld under the backup withholding rules, the non-U.S. holder should consult with a United States tax advisor regarding the possibility of and procedure for obtaining a refund or a credit against the non-U.S. holder's United States federal income tax liability, if any.

FATCA

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

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

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.

Table of Contents**Underwriting**

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC and Credit Suisse Securities (USA) LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them the number of shares indicated below:

Name	Number of shares
Morgan Stanley & Co. LLC	
Credit Suisse Securities (USA) LLC	
Citigroup Global Markets Inc.	
Cowen and Company, LLC	
Total:	2,600,000

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

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

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 390,000 additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 390,000 shares of our common stock.

	Per share	Total	
		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 underwriters for expenses of up to \$ relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc. The underwriters have 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 .

S-19

Table of Contents

We, our directors, our executive officers and Sutter Hill Ventures, a fund affiliated with one of our directors, Jeffrey W. Bird, M.D., Ph.D, have agreed that with the exception of up to 65,000 shares that may be sold pursuant to existing trading plans pursuant to Rule 10b5-1 of the Exchange Act, without the prior written consent of Morgan Stanley & Co. LLC, we and they will not, during the period ending 90 days after the date of this prospectus supplement (the restricted period):

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

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

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

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

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

the sale of shares to the underwriters; or

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

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

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

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

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

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

Table of Contents

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. We understand that Sutter Hill Ventures, a fund affiliated with one of our directors, Jeffrey W. Bird, M.D., Ph.D, plans to distribute a portion of the shares it holds to the managing directors of its general partner, including Dr. Bird, during the lock-up period. Dr. Bird intends to file a Form 4 in connection with the distribution, but the shares of common stock distributed by Sutter Hill Ventures will remain subject to the lock-up.

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

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

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

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the

S-21

Table of Contents

future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling restrictions

European Economic Area

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

- (a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- (b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an offer to the public in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

United Kingdom

The underwriters have represented and agree that:

- (a) they have only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, or FSMA, received by them in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and
- (b) they have complied and will comply with all applicable provisions of the FSMA with respect to anything done by them in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

S-22

Table of Contents

Canada

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

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

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

Table of Contents

Legal matters

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

Experts

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

Where you can find more information

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

Incorporation of certain information by reference

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

our Annual Report on Form 10-K for the year ended December 31, 2014, which was filed with the SEC on March 2, 2015 (the "Form 10-K");

the information specifically incorporated by reference into the Form 10-K from our definitive proxy statement on Schedule 14A which was filed with the SEC on April 30, 2015;

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

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

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

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

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

S-24

Table of Contents

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

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

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

Portola Pharmaceuticals, Inc.

270 E. Grand Ave.

South San Francisco, CA 94080

(650) 246-7000

Attn: Secretary

S-25

Table of Contents

Prospectus

Common Stock

Preferred Stock

Debt Securities

Warrants

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

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

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

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

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

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

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

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

The date of this prospectus is November 9, 2015.

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	i
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	6
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	6
<u>USE OF PROCEEDS</u>	8
<u>RATIO OF EARNINGS TO FIXED CHARGES</u>	8
<u>DESCRIPTION OF CAPITAL STOCK</u>	8
<u>DESCRIPTION OF DEBT SECURITIES</u>	11
<u>DESCRIPTION OF WARRANTS</u>	18
<u>LEGAL OWNERSHIP OF SECURITIES</u>	20
<u>PLAN OF DISTRIBUTION</u>	23
<u>LEGAL MATTERS</u>	25
<u>EXPERTS</u>	25
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	25
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	25
<u>INFORMATION NOT REQUIRED IN THE PROSPECTUS</u>	II-1
<u>SIGNATURES</u>	II-4

ABOUT THIS PROSPECTUS

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

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

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

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different

or additional information. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

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

Table of Contents

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

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

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

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

Table of Contents

PROSPECTUS SUMMARY

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

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

Portola Pharmaceuticals, Inc.

Overview

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

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

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

Table of Contents

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

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

Company Information

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

The Securities We May Offer

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

designation or classification;

aggregate principal amount or aggregate offering price;

maturity date, if applicable;

original issue discount, if any;

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

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

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

Table of Contents

ranking;

restrictive covenants, if any;

voting or other rights, if any; and

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

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

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

the names of those agents or underwriters;

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

details regarding over-allotment options, if any; and

the net proceeds to us.

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

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

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

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

Table of Contents

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

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

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

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

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

Use of Proceeds

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

Proceeds in this prospectus.

Table of Contents

The NASDAQ Global Select Market Listing

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

Table of Contents

RISK FACTORS

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

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

anticipated timing of results from our Phase 3 clinical study of Betrixaban, or APEX;

our anticipated timing of our submission of a Biologics License Application and/or a New Drug Application to the FDA;

our anticipated timing regarding possible commercial launch of our product candidates;

our commercial strategy for commercial launch of our product candidates;

the timing and the success of the design of APEX;

the timing of our Phase 2 proof-of-concept studies of Andexanet alfa;

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

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

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

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

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

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

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

Table of Contents

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

our ability to successfully commercialize our products;

the rate and degree of market acceptance of our products;

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

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

our ability to compete with other commercial Factor Xa inhibitors;

our reliance on third parties to conduct our clinical studies;

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

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

our ability to retain and recruit key personnel;

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

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

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

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

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

our financial performance; and

developments and projections relating to our competitors or our industry.

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

Table of Contents**USE OF PROCEEDS**

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

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

RATIO OF EARNINGS TO FIXED CHARGES

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

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

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

DESCRIPTION OF CAPITAL STOCK**General**

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

directors.

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

100,000,000 shares are designated as common stock; and

5,000,000 shares are designated as preferred stock.

Table of Contents

Common Stock

Voting rights

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

Economic rights

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

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

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

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

Preferred Stock

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

Warrants

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

Table of Contents

Anti-takeover provisions

Certificate of incorporation and bylaws

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

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

The foregoing provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of the company by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change the control of the company.

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

Section 203 of the Delaware General Corporation Law

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

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

Table of Contents

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

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

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

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

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

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

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

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

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

Transfer Agent and Registrar

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

Listing

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

DESCRIPTION OF DEBT SECURITIES

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

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

Table of Contents

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

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

General

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

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

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

the title of the series of debt securities;

any limit upon the aggregate principal amount that may be issued;

the maturity date or dates;

the form of the debt securities of the series;

the applicability of any guarantees;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

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

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

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

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

Table of Contents

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table of Contents

Conversion or Exchange Rights

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

Consolidation, Merger or Sale

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

Events of Default under the Indenture

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

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

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

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

if specified events of bankruptcy, insolvency or reorganization occur.

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

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

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

Table of Contents

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

the direction so given by the holder is not in conflict with any law or the applicable indenture; and

subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

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

the holder has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request;

such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

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

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

Modification of Indenture; Waiver

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

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

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

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

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

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

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

Table of Contents

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

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

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

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

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

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

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

Discharge

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

provide for payment;

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

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

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

maintain paying agencies;

hold monies for payment in trust;

recover excess money held by the trustee;

compensate and indemnify the trustee; and

appoint any successor trustee.

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

Form, Exchange and Transfer

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

Table of Contents

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

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

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

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

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

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

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

Information Concerning the Trustee

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

Payment and Paying Agents

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

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

Table of Contents

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

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

Governing Law

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

DESCRIPTION OF WARRANTS

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

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

General

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

the offering price and aggregate number of warrants offered;

the currency for which the warrants may be purchased;

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

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

Table of Contents

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

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

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

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

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

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

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

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

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

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

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

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

Exercise of Warrants

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

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

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

Governing Law

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

Enforceability of Rights by Holders of Warrants

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

Table of Contents

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

LEGAL OWNERSHIP OF SECURITIES

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

Book-Entry Holders

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

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

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

Street Name Holders

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

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

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

Table of Contents

Legal Holders

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

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

Special Considerations For Indirect Holders

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

the performance of third party service providers;

how it handles securities payments and notices;

whether it imposes fees or charges;

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

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

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

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

Global Securities

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

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

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

Table of Contents

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

Special Considerations For Global Securities

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

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

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

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

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

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

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

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

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

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

matters relating to the securities.

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

Special Situations When a Global Security Will Be Terminated

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

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

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

Table of Contents

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

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

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

PLAN OF DISTRIBUTION

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

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

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

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

the name or names of the underwriters, if any;

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

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

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

any public offering price;

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

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

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

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

Table of Contents

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

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

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

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

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

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

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

Table of Contents

LEGAL MATTERS

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

EXPERTS

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

WHERE YOU CAN FIND MORE INFORMATION

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

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

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

our Annual Report on Form 10-K for the year ended December 31, 2014, which was filed with the SEC on March 2, 2015 (the Form 10-K);

the information specifically incorporated by reference into the Form 10-K from our definitive proxy statement on Schedule 14A which was filed with the SEC on April 30, 2015;

Edgar Filing: PORTOLA PHARMACEUTICALS INC - Form 424B5

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

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

Table of Contents

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

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

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

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

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

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

Portola Pharmaceuticals, Inc.

270 E. Grand Ave.

South San Francisco, CA 94080

(650) 246-7300

Attn: Corporate Secretary

Table of Contents