Raptor Pharmaceutical Corp
Form S-3ASR
October 09, 2015
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As filed with the Securities and Exchange Commission on October 9, 2015

Registration No. 333-

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT

Under

The Securities Act of 1933

Raptor Pharmaceutical Corp.

(Exact name of Registrant as specified in its charter)

Delaware	**86-0883978**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

7 Hamilton Landing, Suite 100

Novato, California 94949

(415) 408-6200

(Address, including zip code, and telephone number, including area code, of Registrant s principal executive offices)

Michael P. Smith

Chief Financial Officer

Raptor Pharmaceutical Corp.

7 Hamilton Landing, Suite 100

Novato, California 94949

(415) 408-6231

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Charles K. Ruck, Esq.

Kathleen M. Wells, Esq.

Latham & Watkins LLP

140 Scott Drive

Menlo Park, California 94025

(650) 328-4600

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. ¨

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. x

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If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. x

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. ¨

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

Large accelerated filer x	Accelerated Filer ¨
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting Company ¨

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price per Security	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee
Common Stock, par value $0.001 per share	**3,448,001(1)**	**$5.77(2)**	**$19,894,965.77(2)**	**$2,003.42**

(1) Pursuant to Rule 416 under the Securities Act of 1933, as amended, or the Securities Act, the shares being registered hereunder include such indeterminate number of shares of common stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions.

(2) Estimated solely for the purpose of calculating the registration fee, and based upon the average of the high and low prices of the Registrant s common stock as reported on the Nasdaq Global Select Market on October 8, 2015

in accordance with Rule 457(c) under the Securities Act.

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PROSPECTUS

3,448,001 Shares

Raptor Pharmaceutical Corp.

COMMON STOCK

This prospectus relates to the offer and resale by the selling stockholders identified in this prospectus of up to an aggregate of 3,448,001 shares of our common stock. We will not receive any of the proceeds from the sale of the common stock by the selling stockholders.

The selling stockholders identified in this prospectus may offer the shares from time to time through public or private transactions at prevailing market prices or at privately negotiated prices. This prospectus provides you with a general description of the securities.

The selling stockholders identified in this prospectus may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If the selling stockholders use underwriters, dealers or agents, we will name them and describe their compensation in a supplement to this prospectus as may be required. We will receive no proceeds from any sale by the selling stockholders of the securities offered by this prospectus, but in some cases we have agreed to pay certain registration expenses. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled About this Prospectus and Plan of Distribution for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES A HIGH DEGREE OF RISK. SEE THE RISK FACTORS SECTION ON PAGE 6 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND THE DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on The Nasdaq Global Select Market under the symbol RPTP. On October 8, 2015, the last reported sale price of our common stock on The Nasdaq Global Select Market was $5.89 per share.

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

The date of this prospectus is October 9, 2015.

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ABOUT THIS PROSPECTUS

You should rely only on the information we have provided or incorporated by reference in this prospectus, any supplement to this prospectus or any free writing prospectus we have authored. Neither we, nor the selling stockholders, have authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. The selling stockholders will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus, the applicable prospectus supplement to this prospectus and any related free writing prospectus that we may provide is accurate as of the date on its respective cover, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

When we refer to Raptor, we, our, us and the company in this prospectus, we mean Raptor Pharmaceutical Corp (including its predecessors) and its consolidated subsidiaries, unless otherwise specified. When we refer to you, we mean the prospective purchasers of the applicable securities.

This prospectus and any accompanying prospectus supplement, including the information incorporated by reference into this prospectus and any accompanying prospectus supplement, and any free writing prospectuses we have authorized for use in connection with any 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 and any accompanying prospectus supplement, and any free writing prospectuses we have authorized for use in connection with any offering, are the property of their respective owners.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

In this prospectus, in other filings with the SEC and in press releases and other public statements by our officers throughout the year, we make or will make statements that plan for or anticipate the future. These forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, include statements about our future business plans and strategies, as well as other statements that are not historical in nature. These forward-looking statements are based on our current expectations.

In some cases, these statements can be identified by the use of terminology such as believes, expects, anticipates, plans, may, might, will, could, should, would, projects, anticipates, predicts, intends, continu opportunity or the negative of these terms or other comparable terminology. All such statements, other than statements of historical facts, including statements regarding our financial condition, future results of operations, projected revenues and expenses, business strategies, operating efficiencies or synergies, competitive positions, growth opportunities for existing intellectual properties, technologies, products, plans and objectives of management, markets for our securities and other prospective matters, involve substantial risks and uncertainties and constitute forward-looking statements for the purpose of the safe harbor provided by Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Such forward-looking statements, wherever they occur, are necessarily estimates reflecting the best judgment of our senior management on the date on which they were made, or if no date is stated, as of the date of the filing made with the SEC in which such statements were made. You should not place undue reliance on these statements, which only reflect information available as of the date that they were made. Our business actual operations, performance, developments and results might differ materially from any forward-looking statement due to various known and unknown risks, uncertainties, assumptions and contingencies, including those described in the section of this prospectus titled Risk Factors as well as other factors not identified therein, and therefore we cannot guarantee future results, levels of activity, performance or achievements and you should not place undue reliance on any such forward-looking statements. We cannot give you any assurance that such forward-looking statements will prove to be accurate and such forward-looking events may not occur. In light of the significant uncertainties inherent in such forward-looking statements, you should not regard the inclusion of this information as a representation by us or any other person that the results or conditions described in those statements or our objectives and plans will be achieved.

All subsequent forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Unless required by U.S. federal securities laws and the rules and regulations of the SEC, we do not undertake any obligation and disclaim any intention to update or release publicly any revisions to these forward-looking statements after the filing of this prospectus to reflect later events or circumstances or to reflect the occurrence of unanticipated events or for any other reason.

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NOTE REGARDING MARKET DATA

We obtained the statistical data, market data and other industry data and forecasts that appears or may appear in this prospectus, any related prospectus supplement or any related free writing prospectus that we may provide and the documents incorporated by reference in this prospectus from sources such as market research reports, publicly available information, industry publications and estimates made by our management. While we believe that this data and these forecasts are reliable, we have not independently verified this information, and we do not make any representation as to the accuracy of this information. We have not sought the consent of the sources to refer to their reports or data appearing or incorporated by reference in this prospectus or any related prospectus supplement or any related free writing prospectus that we may provide.

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WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Section of the SEC at prescribed rates. Further information on the operation of the SEC s Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is http://www.sec.gov.

Our web site address is http://www.raptorpharma.com. The information on our web site, however, is not, and should not be deemed to be, a part of this registration statement.

This prospectus is part of a registration statement that we filed with the SEC and does not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Whenever a reference is made in this prospectus to a contract or other document, the reference is only a summary and you should refer to the exhibits that are a part of the registration statement for a copy of the contract or other document. You may review a copy of the registration statement at the SEC s Public Reference Room in Washington, D.C., as well as through the SEC s website, as provided above.

Incorporation by Reference

The SEC s rules allow us to incorporate by reference information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and, if applicable, supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or any related free writing prospectus that we may provide or any subsequently filed document that is incorporated by reference in this prospectus modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof or exhibits thereto, whether specifically listed below or filed in the future, that are not deemed filed with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC:

- Our Annual Report on Form 10-K for the year ended December 31, 2014, filed with the SEC on March 2, 2015;

The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2014 from our Definitive Proxy Statement on Schedule 14A for the Annual Meeting of Stockholders held on May 5, 2015, filed with the SEC on March 26, 2015;

Our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2015, filed with the SEC on May 7, 2015;

Our Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2015, filed with the SEC on August 6, 2015; and

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Our Current Reports on Form 8-K filed with the SEC on January 7, 2015 (except with respect to Item 7.01 and Exhibit 99.1 furnished under Item 9.01 thereunder), February 13, 2015, April 3, 2015, May 18, 2015, May 20, 2015, July 17, 2015, August 21, 2015 (except with respect to Item 7.01 and Exhibit 99.1 furnished under Item 9.01 thereunder), September 8, 2015, September 8, 2015, September 9, 2015, September 14, 2015 and October 5, 2015.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, excluding any documents or portions thereof or exhibits thereto that are furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Raptor Pharmaceutical Corp.

7 Hamilton Landing, Suite 100

Novato, CA 94949

(415) 408-6200

Attn: Secretary

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus and any accompanying prospectus supplement.

Trademark Notice

Raptor, our logos and all of our product candidates and trade names are our registered trademarks or our trademarks in the United States and in other select countries. Other third-party logos and product/trade names are registered trademarks or trade names of their respective companies.

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SUMMARY

This summary highlights selected information appearing elsewhere in this prospectus or in documents incorporated herein by reference. This summary is not complete and does not contain all of the information that you should consider before making your investment decision. You should carefully read the entire prospectus, including the information set forth in the section entitled Risk Factors and the information that is incorporated by reference into this prospectus. See the sections entitled Available Information and Incorporation by Reference for a further discussion on incorporation by reference.

Overview

We are a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare and debilitating diseases.

Our lead product, PROCYSBI, received marketing approval in the United States from the Food and Drug Administration (the FDA) in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In August 2015, the FDA approved an expansion of the PROCYSBI label to include management of nephropathic cystinosis in children two to six years of age. In Europe, PROCYSBI gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate) received marketing authorization in September 2013 from the European Commission (the EC) as an orphan medicinal product for the management of proven nephropathic cystinosis in the European Union (the EU). The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area, or EEA). PROCYSBI received seven and ten years of market exclusivity due to its designation as an orphan drug in the United States and the EU, respectively. We achieved our first commercial sales of PROCYSBI in the United States in June 2013 and in the EU, specifically in Germany, in April 2014.

In October 2015, we acquired various assets and rights related to levofloxacin solution for inhalation, a pharmaceutical product also known as Aeroquin, MP-376 and commercially as QUINSAIR, from Tripex Pharmaceuticals, LLC (Tripex). QUINSAIR received marketing authorization by the EC for treating long-term lung infection caused by the bacteria Pseudomonas aeruginosa in adults who have cystic fibrosis in March 2015 and Health Canada in June 2015 for the management of cystic fibrosis in patients aged 18 years or older with chronic pulmonary Pseudomonas aeruginosa infections. QUINSAIR is the first inhaled fluoroquinolone approved for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis 18 years old and older. We plan to launch QUINSAIR in Europe and Canada in the first half of 2016. We plan to discuss the path to potential approval in the same indication in the United States with the FDA in 2016 and to initiate clinical programs in at least one of bronchiectasis and nontuberculous mycobacteria in 2016. QUINSAIR is not approved in the United States, and we may not market or commercialize QUINSAIR in the United States for any indication unless and until we receive FDA approval, which we may not be able to obtain.

Marketed Product

PROCYSBI®

PROCYSBI is an approved therapy for the management of nephropathic cystinosis, a rare, life-threatening metabolic lysosomal storage disorder that causes the rapid, toxic accumulation of cystine in all cells, tissues and organs in the body. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a 12-hour dosing period. The enteric-coated beads are pH sensitive and bypass

the stomach for dissolution and absorption in the more alkaline environment

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of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

RP103 Clinical Development Programs

Our two active clinical development programs utilize RP103, which contains the same active pharmaceutical ingredient as PROCYSBI, cysteamine bitartrate. RP103 and PROCYSBI both utilize our proprietary capsule formulation containing delayed-release enteric coated microbeads of cysteamine bitartrate. Cysteamine bitartrate was approved in the United States in 1994 and the EU in 1997 as an orally available immediate-release powder in a capsule for the management of cystinosis. We have an exclusive worldwide license from the University of California, San Diego to delayed-release cysteamine bitartrate, which is the basis for our proprietary formulation of cysteamine. We currently have product candidates in clinical development designed to potentially treat Huntington s disease (HD) and mitochondrial disorders including Leigh syndrome. In September 2015, we announced that the Phase 2b clinical study evaluating the safety and efficacy of RP103 in children with biopsy-confirmed nonalcoholic steatohepatitis (NASH) did not meet its primary endpoint of improving in NASH children, and that we do not expect to advance this program based on topline results.

Huntington s Disease

Huntington s Disease is a rare, inherited neurodegenerative disorder caused by an autosomal dominant mutation in a gene called huntingtin. The huntingtin gene encodes a protein that is also called huntingtin. Expansion of a CAG triplet repeat beyond the normal range within the huntingtin gene results in a mutant form of the protein, which gradually damages cells in the brain. HD causes neuronal degeneration in the cerebral cortex and basal ganglia, which play a key role in movement and behavior control. The cumulative damage to these areas results in the hallmark symptoms of HD: a triad of movement, cognitive and neuropsychiatric symptoms which progress gradually in severity over 15-20 years, eventually causing severe physical and mental disability and premature death. The symptoms of HD usually become evident between ages 35-44 years, but the onset can also begin from childhood to late life (>75 years). The treatment options for HD patients are very limited, with no approved drugs that modify disease course. Recommended treatment strategies consist of drugs for symptomatic relief of chorea, an involuntary motor system (with tetrabenazine, XENAZINE®, approved by the FDA) and mood disorder associated with HD as well as a variety of physical, occupational and dietary therapies.

RP103 as a Treatment for Huntington s Disease

RP103, enteric-coated delayed-release cysteamine bitartrate, is currently being evaluated as a potentially disease modifying treatment for HD. Centre Hospitalier Universitaire France (CHU d Angers), is conducting the Phase 2/3 clinical trial of RP103. This 36-month randomized trial comprises an 18-month blinded, placebo-controlled phase followed by an 18-month open-label phase in which all patients transition to RP103. The primary endpoint of the trial is change from the baseline of the Total Motor Score (TMS) of the Unified Huntington s Disease Rating Scale (UHDRS). TMS, a validated rating scale, is comprised of approximately 15 different tests that evaluate gross and small motor function in patients with HD. Chorea is a single measurement included in the TMS. The trial commenced in October 2010, with full enrollment achieved in June 2012. The study enrolled primarily Stage 1 patients showing early disease symptoms with a UHDRS TMS ³ 5, Total Functional Capacity > 10 and a CAG repeat > 38. Due to the length of the study and the characteristic continuous progression of the disease, patients were allowed to continue their normal medication regime including taking antidepressants and tetrabenazine. Tetrabenazine is approved as a treatment for chorea associated with HD.

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In February 2014, we announced top line results from the planned 18-month analysis of the study. A total of 96 patients with HD were randomized to treatment with RP103 or placebo. A total of 89 patients completed the initial 18-month phase. A mixed model analysis of all 96 patients enrolled in the trial showed slower progression of TMS in patients treated with RP103 versus those patients on placebo after 18 months treatment (4.51 vs. 6.68 respectively, p=0.19). While the results did not reach statistical significance, an overall positive trend was observed.

Patients were not stratified in the study based on concomitant medication use at baseline. We performed post-hoc statistical analyses to assess whether the TMS results were impacted by the effect of tetrabenazine on chorea. In 66 patients not taking tetrabenazine (32 under placebo and 34 under RP103), the results showed a statistically significant difference in the change in total motor score of 2.84 points of progression in the RP103 treatment arm versus 6.78 for the placebo group (p= 0.03).

There were no new or unusual variations from RP103 s clinical safety profile with 48 of 52 patients experiencing at least one adverse event (AE) during the 18-month interim evaluation versus 38 of 44 under placebo. There were slightly more patients under RP103 than under placebo reporting at least one gastrointestinal AE (61.5% RP103 versus 45.5% placebo), which consisted mostly of nausea, vomiting, abdominal pain, constipation, headache and breath odor. There were five patients treated with RP103 who experienced serious adverse events (SAEs) compared with four patients treated with placebo. As of the 18-month time point, seven patients discontinued treatment, six in the RP103 arm and one in placebo. Three patients receiving RP103 discontinued for SAEs including one for lymphopenia, one for repetitive faintness and one for elevated liver enzymes. One SAE in the placebo group, anxiety, resulted in discontinuation. Data from the 36-month time-point for the study is expected in the fourth quarter of 2015.

Under our amended collaboration agreement with CHU d Angers, we supply RP103 and placebo capsules for the clinical trial and open-label extension study and fund the third-party statistical analysis of clinical trial data in exchange for regulatory and commercial rights to the clinical trial data. Clinical expenses of the study are covered by a grant from the Programme Hospitalier de Recherche Clinique, which is funded by the French government.

In 2008, we received FDA orphan drug designation for cysteamine formulations, including RP103, for the potential treatment of HD. We have applied for orphan drug designation in the EU with these topline results.

Mitochondrial Disorders Including Leigh Syndrome

Leigh syndrome is a severe neurological disorder caused by genetic defects in mitochondrial or nuclear DNA affecting respiratory chain function that typically results in death within the first decade of life. The condition causes increased production of reactive oxygen species that disrupt mitochondrial electron transport and affect cellular function in a variety of tissues. Typically observed during the first year of life, Leigh syndrome is characterized by a failure to thrive, lack of coordination, involuntary and sustained muscle contraction, muscle wasting and multiple organ failure. The incidence of Leigh syndrome in the United States is estimated to be 1 in 40,000 newborns.

RP103 as a Treatment for Mitochondrial Disorders including Leigh Syndrome.

In June 2014, we initiated a Phase 2 study in the United States designed to evaluate the safety, tolerability and efficacy of RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders. RP103 potentially increases mitochondrial glutathione which may act as a scavenging agent of reactive oxygen species and thereby reduce the mitochondrial oxidative stress typically associated with these disorders.

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The clinical plan includes an open label, 24 week, Phase 2/3 study in 24 patients (up to a maximum of 32 patients). Patients with Leigh syndrome are expected to comprise two-thirds of the enrolled population in the study. Based on an adaptive design statistical plan, we will conduct interim analyses after four patients and again after 12 patients have completed the study to determine final sample size. The primary endpoint of the study will be the change from baseline in the Newcastle Pediatric Mitochondrial Disease Scale, at 24 weeks. Secondary endpoints will include observations of myopathy, dystonia, seizures, motor development, dyskinesia, quality of life and activities of daily living. Interim results from the clinical trial are expected by the end of 2015.

Other Clinical-Stage Product Candidates

Our other current clinical-stage product candidate is Convivia®, our proprietary oral formulation of 4-methylpyrazole, for the potential management of acetaldehyde toxicity due to alcohol consumption by individuals with aldehyde dehydrogenase (ALDH2) deficiency, an inherited metabolic disorder.

Preclinical Product Candidate Programs

Our preclinical programs include our cysteamine dioxygenase, or ADO, program and our HepTide program designed to potentially treat hepatocellular carcinoma and other cancers susceptible to induced lysosomal storage.

Future Activities

Over the remainder of the fiscal year, our efforts will be focused on increasing sales of PROCYSBI in the United States and Europe; launching or providing access to PROCYSBI in other countries in the EU and other select countries around the world; maintaining progress on filing a New Drug Submission for cysteamine bitartrate delayed-release capsules with Health Canada; conducting a clinical trial to evaluate PROCYSBI in cystinosis patients that are cysteamine-naïve, as well as other supporting trials in underdeveloped markets; screening for undiagnosed and unidentified adult nephropathic cystinosis patients; supporting regulatory pathways and/or clinical trials of RP103 for the potential treatment of HD, Leigh syndrome and mitochondrial disorders; preparing to launch QUINSAIR in Europe and Canada in the first half of 2016 and preparing to initiate clinical programs in at least one of bronchiectasi and nontuberculous mycobacteria; enhancing and expanding our product manufacturing capabilities; preparing for potential clinical studies of RP103 in new therapeutic indications; supporting our novel preclinical programs; seeking additional business development partners in Asia for our Convivia product candidate; and developing new preclinical, clinical and or commercial opportunities, including novel proprietary product candidates, technologies or products identified and acquired through business development activities.

Corporate Information

We are incorporated under the laws of the State of Delaware and our business was founded in May 2006. Our principal executive office is located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our phone number is (415) 408-6200.

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The Offering

Issuer	Raptor Pharmaceutical Corp.
Selling stockholders	Selling stockholders named in this prospectus and any of their pledgees, donees, transferees, assignees or other successors-in-interest. See the section entitled Selling Stockholders.
Securities offered by selling stockholders	3,448,001 shares of our common stock.
Use of proceeds	We will not receive any proceeds from the sale of shares by the selling stockholders.
Risk factors	This investment involves a high degree of risk. See Risk Factors on page 6 of this prospectus and other information we include or incorporate by reference in this prospectus.
Nasdaq Global Select Market symbol	RPTP

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RISK FACTORS

An investment in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should consider carefully all of the information in this registration statement, including the risks and uncertainties described below, as well as other information included in or incorporated by reference into this registration statement, particularly the specific risk factors discussed in the sections titled Risk Factors contained in our filings with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, before deciding whether to invest in our common stock. Any of these risks could have a material adverse effect on our business, prospects, financial condition and results of operations. In any such case, the trading price of our common stock could decline and you could lose all or part of your investment.

Risks Associated with Commercialization and Product Development

Our revenues currently depend entirely on the commercial success of our lead drug, PROCYSBI, for the management of nephropathic cystinosis.

PROCYSBI is our only product that is currently marketed, and as a result, our revenue and operating results substantially depend on the continued commercial success of PROCYSBI. We commenced marketing for PROCYSBI in the United States in June 2013 and Europe in April 2014. In the United States, we are permitted to market PROCYSBI for the management of nephropathic cystinosis in adults and children two years and older. In September 2013, we received marketing authorization from the European Commission (EC) to commercialize PROCYSBI for the treatment of proven nephropathic cystinosis in the European Economic Area (EEA). We commenced commercial sales of PROCYSBI in Germany in April 2014 and have launched commercial sales in select additional countries in Europe. We have no assurance of securing reimbursement and subsequently launching in additional countries in the EEA. We believe that our results of operations and, in particular, our net product sales of PROCYSBI will affect the trading price of our common stock substantially. If PROCYSBI sales do not meet market expectations, our stock price may fluctuate and may significantly decrease.

Our ability to successfully commercialize our current and any other future drug products will depend on multiple factors, including:

- our ability to provide acceptable evidence of the safety and efficacy of our products;
- compliance with regulatory requirements, including fulfilling post-approval commitments;
- our ability to obtain approval by regulatory agencies in other countries, including appropriate product labeling;
- the effect of current and future healthcare laws;
- the manufacture and supply of adequate quantities of our products in compliance with current good manufacturing practices as needed to meet commercial demand;

adequate coverage and reimbursement for our products from commercial health plans and government health programs, which we refer to collectively as third-party payors ;

our ability to obtain acceptable prices in EEA countries and other select territories, including acceptable reimbursement at the country-specific price;

limitations or warnings currently contained in or as may later be required in approved labeling and the breadth of product labeling or product insert requirements;

our ability to enter into agreements with wholesalers, distributors and pharmacies on commercially reasonable terms; and

the protection, development and maintenance of intellectual property and other commercial product protection for our products.

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If we fail to grow sales of PROCYSBI in existing markets, to successfully sell PROCYSBI in other countries or to successfully commercialize QUINSAIR or any other future products within a reasonable time period, we will have reduced financial resources and may be unable to fully execute our business plans, and our results of operations and financial condition will be materially adversely affected.

Our ability to generate significant product sales from our products is dependent upon market acceptance among physicians, patients, patient families, third-party payors and the healthcare community.

Our current and any future drug products may not attain or maintain market acceptance among physicians, patients, patient families, third-party payors or the healthcare community compared to the current and evolving standards of care and to standards of care from new competitors. We believe that the degree of market acceptance and our ability to generate significant product sales of our current and any future drug products will depend on a number of factors, including:

- the efficacy, safety, availability and ease of administration of our products relative to alternative treatments;
- the price of our products, both in absolute terms and relative to the quality of therapeutic benefits and price of alternative treatments;
- the timing of market introductions of our products and product lines relative to competitive drugs;
- the nature of publicity related to our products relative to the publicity related to our competitors products;
- the prevalence and severity of adverse side effects of our current and any future products;
- good patient compliance to therapy;
- availability of coverage and adequate reimbursement from third-party payors;
- provision of affordable out-of-pocket costs to patients and/or other programs to ensure patient access to our products; and
- the identification of currently diagnosed and undiagnosed patients and continued growth of the cystinosis and cystic fibrosis markets and the markets for any other future products.

Our efforts to educate patients, physicians, parents, the medical community and third-party payors on the benefits of our products may require significant resources and may not be successful at the levels planned. If our products do not achieve and maintain significant market acceptance among physicians, patients, patient families, third-party payors and the healthcare community, our business, results of operations and financial condition will be materially adversely

affected.

The amount of our product sales in the EEA are dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our products due to budgetary decisions made by regional, national and local health authorities and third-party payors in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market PROCYSBI, to bring QUINSAIR to market and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our products.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging,

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distribution, storage, adverse event reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of product registration and continued compliance with good manufacturing practices, or GMPs, good clinical practices, or GCPs, good pharmacovigilance practice, or GPVs, good distribution practices, or GDPs, and good laboratory practices, or GLPs. We are in the process of implementing corrective and preventive actions related to our pharmacovigilance system to address findings following a routine inspection from a European regulatory authority.

If we, our products or product candidates, or the third-party manufacturing facilities for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose restrictions on the marketing or manufacturing of a product, suspend or withdraw product approvals, revoke necessary licenses or suspend product reimbursement;
- impose injunctions, suspensions or revocations of necessary approvals or other licenses;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain products or require us to initiate a product recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our products may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the products. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, European Medicines Agency (EMA), European Commission (EC) and

other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription products, and our product labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our products to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our product development programs increase the risk that approved pharmaceutical forms of the same active pharmaceutical ingredients may be used off-label in those indications. Our investigational product candidate RP103 is comprised of the same active pharmaceutical ingredient as PROCYSBI. If we are found to have improperly promoted off-label uses of approved products, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our products for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or

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Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act (FDASIA), requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company s responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we may not be permitted to market our drugs, which would adversely affect our ability to generate revenue and achieve or maintain profitability.

If we are unable to expand the use of RP103 or MP-376 pursuant to regulatory approval for additional clinical indications or geographic territories, or are unable to obtain regulatory approval for other product candidates, we may delay or terminate some of our product development activities. This could adversely affect the long term value of RP103, MP-376 or other product candidates as well as our growth prospects.

The research, testing, manufacturing, clinical development, labeling, approval, sale, marketing and distribution of drug products, among other things, are subject to extensive regulation by the FDA and other regulatory authorities in the United States and by similar foreign governmental regulatory entities. We are not permitted to market any of our drug product candidates unless we obtain and maintain appropriate marketing approvals from regulatory agencies in each of the markets in which we intend to market our products. Once approved, we may only market our products for the specific uses that are reflected in the product s approved labeling. A product s approved labeling may contain limitations or warnings or may be for different patient populations or for fewer or more limited indications than we request in our pre-market approval application, which could result in limiting reimbursement, access for intended use or the commercial profile of a drug. In the United States, we are permitted to market the active pharmaceutical ingredient of RP103 in the formulation of a final drug product and in the doses approved under the brand name PROCYSBI only for the management of nephropathic cystinosis in adults and children two years and older. We are permitted to market PROCYSBI in the EEA as an orphan medicinal product for the treatment of proven nephropathic cystinosis. MP-376 has been approved for marketing in Canada and the EEA under the specific indication as a medicinal product for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults 18 years and older with cystic fibrosis. Neither RP103 nor MP-376 has been approved in any other market or for any other disease indication. There can be no assurance that we will obtain regulatory approval for any other uses for our product candidates or that, even if we obtained additional approvals, we would be able to commercialize the product candidates successfully.

A new drug application (NDA), submitted to the FDA, or a marketing authorization application (MAA), submitted to the EMA, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls. This information must demonstrate the safety and efficacy of the applicable product candidate for the management of each individual indication to the satisfaction of the applicable regulatory authority. Obtaining approval of an NDA, MAA or any other filing for marketing authorization in a foreign country for a drug product candidate is an extensive, expensive and uncertain process. The time required to obtain approval by

the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors,

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including the substantial discretion of the regulatory authorities. The FDA, EC or other regulatory authorities may delay, limit or deny approval of RP103, MP-376 or our future drug product candidates for many reasons, including:

- the results of clinical trials may not meet the level of statistical or clinical significance required by regulatory authorities for approval;

- regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials; they may change the requirements for approval even after having reviewed and commented on the design for our clinical trials;

- regulatory authorities may not find the data from preclinical studies and clinical trials sufficient to demonstrate that product candidates have adequate clinical and other benefits or adequate safety profiles, even if they achieve their specified endpoints in clinical trials; or they may disagree with our interpretation of data from preclinical studies or clinical trials and/or require that we conduct additional trials;

- regulatory authorities may not accept data generated at our clinical trial sites;

- if requested by us, regulatory authorities may not hold an advisory committee meeting in a timely manner or at all, or, if an advisory committee is convened it may recommend against approval of our application or may recommend that the regulatory agency require, as a condition of approval, additional preclinical studies or clinical trials; approval may also be contingent on a Risk Evaluation and Mitigation Strategy, which limits the labeling, distribution or promotion of a drug product;

- regulatory authorities may require additional preclinical or clinical studies or other data prior to granting approval, and we may not be able to generate the required data on a timely basis, if at all;

- regulatory authorities may identify deficiencies in the manufacturing processes or in the facilities of our third-party suppliers and/or contract manufacturers or may require us to manufacture additional validation batches or change our submitted regulatory documents, process, specifications or third-party suppliers or contract manufacturers; and

- we may not be able to validate manufacturing processes to the satisfaction of the regulatory authorities.

With respect to QUINSAIR, the FDA has indicated in previous written communications that it believes the clinical and non-clinical data submitted in connection with the EMA s approval of MP-376 for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis does not provide substantial evidence of efficacy and safety to support FDA approval of MP-376 for treatment of patients with cystic fibrosis. The FDA identified a number of limitations with the design of the study that, in the FDA s view, impact its ability to be used as a pivotal efficacy study. The FDA also questioned whether patients in the study achieved any overall benefit, as the primary endpoint in the study was not met. We intend to discuss potential registration strategies with the FDA.

We may not agree with the developmental pathway that the FDA recommends or be able to conduct the clinical trials that the FDA requests, which could limit our ability to seek regulatory approval for MP-376 in the United States.

If we fail to gain regulatory approval for RP103 or MP-376 for other indications, in additional geographic jurisdictions, or for our other future drug product candidates, we will have to delay or terminate some or all of our research product development programs, and our business, results of operations and financial condition will be materially adversely affected.

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We do not have internal manufacturing capabilities. Throughout the remainder of 2015, we expect to continue to rely on a single source supplier for our active pharmaceutical ingredient (API) for PROCYSBI and a single third-party manufacturer for the conversion to finished commercial drug product. Similarly, we expect to utilize single source suppliers for the QUINSAIR API, drug product and delivery device, upon commercial launch. We also rely on third parties for the distribution and pharmaceutical services of PROCYSBI in the United States and the EEA. If we are unable to rely on these third parties, our revenue will be delayed or diminished and our business, results of operations and financial condition will be materially adversely affected.

We do not own or operate manufacturing facilities and currently lack the in-house capability to manufacture our current products or product candidates. As a result, we currently contract with external contract manufacturing organizations (CMOs), for commercial and clinical quantities of our products for the indications under development. We rely on a single source supplier for our cysteamine API. While we have procured additional manufacturing support with a second provider for clinical supply of PROCYSBI, for the remainder of 2015, we will continue to rely on a single third-party manufacturer for supply of finished commercial product until a second supplier can be validated and provide finished product. Our ability to obtain sufficient quantities of PROCYSBI and RP103 is constrained by limited supplies of raw materials and the limited capacity and output of these third parties. Furthermore, any reduction, delay or interruption in our supply of APIs from the single source supplier or of our supply of finished goods from our CMOs, together with any additional required efforts to identify and qualify alternative sources of API supply, could result in significant additional operating costs, interruptions in product supply, delays in sales of PROCYSBI, delays in the commercial launch of QUINSAIR, and delays in developing RP103 and MP-376 for additional indications. In addition, supply arrangements from alternative sources not currently under contract may not be available on acceptable economic terms, if at all.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production volume to commercial requirements. Difficulties may arise related to internal processes, production costs and yields, quality control, including stability of the product and quality control testing, sourcing scarcities, resource constraints, equipment problems, shortages of qualified personnel, labor disputes, severe weather events, unstable political environments or financial difficulties at foreign facilities, as well as compliance with strictly enforced federal, state and foreign regulations. Manufacturers may breach their agreements with us or may terminate or decline to renew their agreements with us, whether due to our breach of the relevant agreements or based on their own business priorities. In addition, due to our small patient population, the manufacturers of our drug may be given lower prioritization on the production line if manufacturing prioritization is decided by scale.

Manufacturers and suppliers are subject to regulatory requirements covering, among other things, manufacturing, process controls, testing, quality control and record keeping and are subject to ongoing inspections by regulatory agencies. We have no direct control over the ability of our contract manufacturing parties to maintain adequate quality control, quality assurance and qualified personnel, and while final outputs are reviewed by our own internal quality control, we depend on our third-party supplier and manufacturers for compliance with the FDA s current cGMP requirements and other FDA requirements, the Drug Enforcement Administration s regulations and other rules and regulations prescribed by applicable non-U.S. regulatory authorities. If our contract manufacturing partners cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to supply manufactured product to us and they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities, and we may experience long delays and interruptions to our manufacturing supply and increased costs.

Pursuant to ongoing obligations from the NDA for PROCYSBI, we are required to collect and submit data to the FDA regularly regarding our currently observed clinical and commercial product profile and overall product safety assessment. Similarly, pursuant to obligations in the MAA for QUINSAIR, we will be required to

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conduct post-marketing clinical studies in cystic fibrosis patients and submit data to the EMA regularly regarding observed clinical product profile and safety assessment. In addition, we intend to continue to evaluate our product specification limits, and any changes to our product specifications may require additional review and approval by regulators in the United States and Europe. If there are material delays in any such review and approval process, or if regulators reject any proposals for changes in product specifications or require additional data to support the updated specifications, we may experience an inventory shortfall, which would have a material adverse effect on sales of our products.

If we or our third-party suppliers and manufacturers fail to comply with applicable regulatory requirements, we could experience significant delays or interruptions to our manufacturing supply that may result in the delay or suspension of our preclinical or clinical trials. In addition, a regulatory agency could issue warning letters or untitled letters, seek an injunction, impose civil or criminal penalties or monetary fines, suspend or withdraw regulatory approval, require specification changes, suspend any ongoing clinical trials, refuse to approve pending applications or supplements to applications, suspend or impose restrictions on operations, including costly new manufacturing requirements, seize or detain products or request that we initiate a product recall.

We also rely on a third-party logistics provider and specialty pharmacy to distribute PROCYSBI to patients in the United States and to pharmacies in the EEA and to collect from insurance companies and government agencies in the United States and from pharmacies in the EEA. We plan to employ a similar network of third-party services providers to distribute QUINSAIR in the EEA and Canada. Our ability to collect from a particular logistics provider is not only subject to such provider s credit worthiness but is also dependent, in part, on its ability to arrange for full reimbursement from third-party payors. The outsourcing of our distribution function is complex, and we may experience difficulties that could reduce, delay or stop shipments of our products. If we encounter such distribution problems, and we are unable to quickly enter into a similar agreement with another specialty distributor on substantially similar terms, if at all, the distribution of our products could become disrupted, resulting in reduced revenues, healthcare provider dissatisfaction and/or patient dissatisfaction, which may materially adversely affect our business, results of operations and financial condition.

If any of these events were to occur, our reputation would be harmed, revenues from sales of our products would be delayed or diminished and our business, results of operations and financial condition would be materially adversely affected.

If serious adverse side effects become associated with our current or future products, our business, results of operations and financial condition will be materially adversely affected.

The prescribing information for both PROCYSBI and QUINSAIR include several warnings relating to observed adverse reactions of the active pharmaceutical ingredient usage. The FDA may require products approved under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (the FDCA) to bear the same or similar warning statements as the reference product used in the approval. We expect to update adverse reactions listed in the prescribing information for our products based on continued commercial use and additional clinical trials. If additional adverse reactions emerge, or if there is a pattern of severe or persistent previously observed side effects in the relevant patient populations, the FDA, the European Medicines Agency (the EMA) or other regulatory agencies could modify or revoke our marketing approvals, require us to modify our labels or require us to suspend production, require a product recall, or we may choose to withdraw a product from the market.

Regulatory authorities could also require us to change the way our products are administered or modify a product in some other way, or they could require us to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of our products. If this were to occur, we may be unable to maintain

marketing approvals in our approved indications and/or obtain marketing approval in other indications. In addition, patients or their representatives may bring claims against us alleging serious adverse side effects or harm suffered as a result of use of our products. Any such side effects or related claims could have a

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material adverse effect on our business, results of operations and financial condition. See also the risk factor titled *We may be subject to product liability claims*.

If we fail to demonstrate safety or efficacy in our preclinical studies or clinical trials or to keep to the terms of a product development program, our future business prospects for our drug product candidates will be materially adversely affected.

Clinical trials are very expensive, time consuming and difficult to design and implement. The outcome of clinical trials is uncertain, and results of earlier studies and trials may not be predictive of future trial results. Delays in the commencement or completion of clinical or preclinical testing for RP103 or MP-376 or any of our other product candidates could significantly affect our product development costs and business plan.

Preclinical studies involve testing in multiple non-human disease models to demonstrate efficacy and safety. Regulatory agencies evaluate these data carefully as part of their determination whether to authorize clinical testing in humans. If certain preclinical data reveal potential safety issues or if the results are inconsistent with an expectation of the drug product candidate s efficacy in humans, the regulatory agencies may require additional testing before allowing human clinical trials. This additional testing will increase program expenses and extend timelines. There are many potential preclinical models to test for different disease states, and we could fail to choose the best or a predictive preclinical model to determine proof of concept, safety and efficacy of our drug product candidates. We may decide to suspend further testing on our drug product candidates or technologies if, in the judgment of our management and advisors, the preclinical test results do not support further development. Following successful preclinical testing, drug product candidates must be tested in a clinical development program to provide data on safety and efficacy in humans prior to becoming eligible for product approval and licensure by regulatory agencies. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials.

Clinical trials may also be delayed or repeated as a result of ambiguous or negative interim results or unforeseen complications in testing. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. The clinical trial process may fail to demonstrate with statistical significance that our drug product candidates are safe for humans and effective for indicated uses. This failure may cause us to abandon a drug product candidate and may delay development of other drug product candidates. Any delay in, or termination of, our preclinical testing or clinical trials will delay the filing of relevant marketing applications with regulatory agencies and, ultimately, our ability to commercialize our drug product candidates and generate revenues from related products.

The rate of completion of any clinical trials will be dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the trial, the nature of the disease or medical condition being studied, the availability of alternative therapies and drugs, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays. In addition, because many of our clinical trials involve small patient populations, the results of these early clinical trials may not be indicative of future results. Further, the timing of regulatory approval of clinical trial applications by local regulatory agencies or ethics committees may also affect the initiation of trial sites and therefore the rate of patient enrollment.

Under the Prescription Drug User Fee Act, the FDA seeks to respond to NDAs within ten months of the filing date, but this timeframe is often extended. For example, a sponsor may seek FDA designation of a drug candidate as a fast track product. Fast track products are those products intended for the treatment of a serious or life-threatening disease

or condition and which demonstrate the potential to address unmet medical needs for such disease or condition. If fast track designation is obtained, the FDA may initiate review of sections of an NDA before the application is complete. This rolling review is available if the applicant provides and the FDA

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approves a schedule for the remaining information. In addition, FDASIA established a new category of drugs referred to as breakthrough therapies, which are defined as drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. In the future, we may request breakthrough designation or fast track designation from the FDA for our other drug product candidates, but there can be no assurance that we will obtain such designations. Moreover, even if we obtain breakthrough designation or fast track designation from the FDA, the designations do not guarantee that the FDA will approve our NDA, that the development program or review timeline will ultimately be shorter than if we had not obtained the designations or that the FDA will not request additional information, including additional clinical studies, during its review.

We do not know whether our investigational new drug, or IND, applications for future products or the protocols for any future clinical trials will be accepted by the FDA or EMA. We do not know if our clinical trials will begin or be completed on schedule or at all. Even if completed, we do not know if these trials will produce clinically meaningful results sufficient to support an application for marketing approval. The commencement and completion of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with particular types of disease for enrollment in clinical trials;
- delays or failures in obtaining regulatory clearance to commence a clinical trial;
- delays or failures in obtaining sufficient clinical materials;
- inability to design appropriate clinical trial protocols;
- delays or failures in reaching agreement on acceptable clinical trial agreement terms or clinical trial protocols with prospective sites;
- inability of our clinical research organizations (CROs), or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
- inability by us, our CROs or their employees to conduct the clinical trial in accordance with all applicable FDA, Drug Enforcement Administration or other regulatory requirements or our clinical protocols;
- lack of efficacy during, or other unfavorable results from, clinical trials or preclinical studies;

discovery of serious or unexpected toxicities or side effects experienced by study participants or other unforeseen safety issues;

failure of patients to complete the clinical trial, or inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;

inability to monitor patients adequately during or after treatment;

regulatory action by the FDA or other regulatory authorities; and/or

lack of adequate funding to continue the clinical trial, including the incurrence of any unforeseen costs.

In addition, changes in applicable regulatory requirements and guidance may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to Institutional Review Boards for reexamination, which may affect the costs, timing or successful completion of a clinical trial.

Sales of our products outside of the United States are also subject to foreign regulatory requirements governing clinical trials, manufacturing and marketing approvals. Even if the FDA and EC grant marketing

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approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of our product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials or manufacturing and control requirements. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In many cases, the price that we propose to charge for our products is also subject to approval by individual countries before we can launch our product candidates in those countries. Obtaining foreign regulatory approvals, complying with foreign regulatory requirements and gaining approved pricing and reimbursement could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others.

Any delay in our preclinical or clinical programs or the failure to demonstrate safety or efficacy in our clinical trials would have a material adverse effect on our business, results of operations and financial condition.

If we fail to maintain orphan drug or other regulatory exclusivity for our products or to obtain and maintain exclusivity for our orphan drug product candidates, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.

PROCYSBI received marketing approval from the FDA for the management of nephropathic cystinosis in adults and children two years and older and seven years of market exclusivity as an orphan drug in the United States. PROCYSBI has also received approval as an orphan medicinal product for the management of proven nephropathic cystinosis and 10 years of market exclusivity in the EEA. QUINSAIR received marketing approval from the EMA in 2015 for management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis. In the United States, the FDA has designated QUINSAIR as an orphan drug for treatment of pulmonary infections due to *Pseudomonas aeruginosa* and other bacteria in patients with cystic fibrosis. As part of our business strategy, we intend to develop RP103 and MP-376, and potentially other drugs, for additional therapeutic indications that may be eligible for FDA and EMA orphan drug designation.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years, plus an additional six months if designated for a pediatric indication.

In the EU, the EMA s Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or if the product would be a significant benefit to those affected). In addition, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition as well as when it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product without incentives. An EU orphan drug designation entitles a party to financial incentives such as reduced fees or fee waivers,

and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. An applicant must request orphan drug designation before submitting an application for marketing

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approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Even though we have been granted orphan drug designation in the United States and in the EU prior to the approval of RP103 for the potential treatment of Huntington s Disease (HD), and even if we obtain orphan drug designation for our future drug product candidates, we may not fulfill the criteria for exclusivity, or we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a particular product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective, if a subsequent product is deemed clinically superior or if the manufacturer is unable to deliver sufficient quantities of the drug.

Because the extent and scope of patent protection for some of our drug products may be particularly limited, orphan drug designation is especially important for our eligible products and we plan to rely on the orphan or other regulatory exclusivity period to maintain a competitive position. However, if we do not obtain and/or maintain orphan drug exclusivity for our drug products, or if our drug products do not have strong patent protection, our competitors may sell the same drug to treat the same condition, possibly at lower prices, and our revenues will be reduced. Also, without strong patent protection, competitors may sell a generic version of our products upon the expiration of orphan exclusivity if our patent position is not upheld.

If our competitors succeed in developing products and technologies that are more effective than our own, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive.

We face significant competition from industry participants that are pursuing technologies similar to those that we are pursuing and are developing pharmaceutical products that are competitive with our products or our product candidates. Many of the pharmaceutical companies in areas competitive with us have greater capital resources, larger overall research and development staff and facilities and a longer history in drug discovery, development, regulatory approval, manufacturing and marketing than we do. With these additional resources and experience, our competitors may be able to respond to rapid and significant technological changes in the biotechnology and pharmaceutical industries faster than we can.

We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies. Rapid technological development, as well as new scientific developments, may result in our compounds, drug products, drug product candidates or processes becoming obsolete before we can recover any or all of the expenses incurred to develop them. For example, changes in our understanding of the appropriate population of patients who should be treated with a targeted therapy like those we are developing may limit the drug s market potential if it is subsequently demonstrated that only certain subsets of patients should be treated with the targeted therapy.

No human clinical data has been generated to validate the use of MP-376 to treat non-tuberculous mycobacteria infection (NTM) or in bronchiectasis (BE).

We intend to develop MP-376 for use in at least one of non-tuberculous mycobacteria infection or brochiectasis, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No human clinical data has been generated with MP-376 with these specific pathogens in NTM or BE, either by us or by other parties. This creates substantial uncertainty as the efficacy of

MP-376 in these indications. Successful completion of well-controlled clinical trials of adequate size is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of MP-376 or any other potential product candidate in these indications. A

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failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later preclinical testing or clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products from regulatory authorities.

The approval of any product or product candidate, including QUINSAIR, in any given market does not ensure approval in any other market.

In order to market any product candidate, we must establish and comply with numerous regulatory requirements on a country-by-country basis regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation, and additional administrative review periods. As a result, international regulatory requirements could delay or prevent the introduction of our products and product candidates across different countries. For example, approval of QUINSAIR in the EEA and Canada does not ensure approval by the FDA or regulatory authorities in other countries or jurisdictions, nor does it ensure approval for the same conditions of use. Further, seeking U.S. regulatory approval for QUINSAIR could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products and product candidates will be unrealized.

We have obligations to Tripex to conduct certain regulatory and development activities with respect to QUINSAIR. Delays or other factors that prevent us from completing these regulatory and development activities may put us in breach of our obligations to Tripex.

The terms of our asset purchase agreement for the acquisition of QUINSAIR require us to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial in a non-cystic-fibrosis patient population within a specified period of time. These terms also require us to progress toward filing an NDA for approval of QUINSAIR in the United States in all or part of the cystic fibrosis patient population within a specified period of time. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to file an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the asset purchase agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex.

Because the target patient populations for our products and some of our drug product candidates are small, we must achieve significant market share and obtain sufficient per-patient prices for our products to achieve meaningful gross and operating margins.

PROCYSBI, QUINSAIR and clinical development of RP103 and MP-376 target rare diseases with small patient populations, including cystinosis, cystic fibrosis, mitochondrial disorders including Leigh s Disease, NTM, BE and HD. To successfully commercialize a drug product for these indications, we must identify patients and a targeted prescriber base for each drug product. Due to small patient populations, we believe that we would need to have significant market penetration to achieve meaningful revenues. In addition, the per-patient prices at which we sell our current products for these indications may need to be relatively high in order for us to generate an appropriate return

on the investment in our product development programs and to achieve meaningful gross and net operating margins. Patients who discontinue therapy or do not fill prescriptions are not easily replaced by new patients because of the limited patient populations. There can be no assurance that we will successfully

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obtain or maintain sufficient market share or per-patient prices. Because our current potential target populations are very small, even if we obtain significant market share for our current or future products and product candidates, we may never achieve profitability despite obtaining such significant market share.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by the Centers for Medicare & Medicaid Services (CMS), and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors in connection with drugs, including PROCYSBI, that are dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The terms, scope and complexity of these government pricing programs change frequently. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming. See also the risk factor titled *Legislative changes regarding manufacturers rebate obligations for new formulations of oral solid dosage form drugs under the Medicaid Drug Rebate Program, if applied to PROCYSBI, would have a material adverse effect on our business, results of operations and financial condition.*

In addition, the Office of Inspector General has recently increased its focus on the methodologies used by manufacturers to calculate average manufacturer price (AMP), and best price (BP), to assess manufacturer compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In the event that the CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

Pricing and reimbursement policy changes from third-party payor coverage may impair our customers ability to be reimbursed for our products and product candidates at adequate prices or on adequate terms, which may in turn materially adversely affect our business, results of operations and financial condition.

Market acceptance and sales of our products will depend in large part on third-party payor coverage and reimbursement policies and may be affected by future healthcare reform measures in the United States, the EEA and other key international markets. The continuing efforts of governmental and other third-party payors to contain, reduce or shift the costs of healthcare through various means, including an increased emphasis on managed care and attempts to limit or regulate the price of medicinal products and services, particularly for new and innovative products and therapies, may result in downward pressure on pricing, reimbursement and utilization, which may adversely affect our product sales and results of operations. Moreover, because private health insurers and other third-party payors often follow the coverage and reimbursement policies of government payors, including the Medicare and Medicaid

programs, cost-containment measures under these programs play a

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particularly significant role in the reimbursement landscape. The government programs relevant to our products include, without limitation, the following:

- the Medicaid Drug Rebate Program, under which manufacturers must report pricing information and pay rebates in order for their drug products to be covered under state Medicaid programs;
- the Public Health Service s 340B Drug Pricing Program, under which manufacturers must offer discounts to certain healthcare organizations that care for underserved populations;
- the Department of Veterans Affairs Federal Supply Schedule pricing program, under which manufacturers agree to offer drugs to certain governmental providers at reduced rates;
- the TRICARE Retail Pharmacy Program, under which manufacturers must agree to honor certain discounted prices, specifically Federal Ceiling Prices under the Veterans Health Care Act, as a condition for placement in the Department of Defense uniform formulary; and
- the Medicare Part D program, under which manufacturers contract with plan sponsors to offer certain outpatient drugs to Medicare beneficiaries.

In addition, in the United States, third-party payors often develop cost containment measures using policies that specifically target specialty products and high-cost drugs. For example, formulary placements may be less favorable for brand and higher-costing drugs, which may result in, among other things, greater out-of-pocket costs to patients. PROCYSBI often is subject to such measures, and similar future policies addressing such cost-containment measures may also affect PROCYSBI.

Further, third-party payors also are increasingly considering new metrics as the basis for reimbursement rates, such as average sales price, AMP or actual acquisition cost, and for cost-benefit analyses with comparable drugs. Although the changes to reimbursement methodologies are generally intended to limit payment increases, it is difficult to project the impact of these and other alternative reimbursement methodologies on the willingness of payors to reimburse for our products and any product candidates that we may develop. To date, PROCYSBI generally has been covered and reimbursed commercially in the United States and the select countries in which we have sold PROCYSBI worldwide, but we do not know whether third-party payors will continue to cover and reimburse PROCYSBI in these markets or at the level PROCYSBI is currently covered, will reimburse PROCYSBI in other EEA countries or will reimburse our future products until we enter into payor negotiations. If coverage and reimbursement are not available or limited, or reimbursement is available only at limited levels, our business, results of operations and financial condition will be materially adversely affected.

Legislative changes may increase the difficulty and cost for us to commercialize our products or any other product candidate that we develop and affect the prices we may obtain.

In the United States, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that restrict or regulate post-approval activities. The changes may affect our ability to sell PROCYSBI or any other product candidate for which we obtain marketing approval at adequate prices.

In 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, which we refer to together as the Affordable Care Act, was adopted. This law intends to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The Affordable Care Act, among other things:

increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program;

revised the definition of AMP for reporting purposes, which could further increase the amount of rebates paid by manufacturers under the Medicaid Drug Rebate Program;

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extended the Medicaid Drug Rebate Program to beneficiaries enrolled in Medicaid managed care organizations;

addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected and for oral solid line extensions and reformulated drugs, which, depending on how the provision is interpreted and implemented, could increase our Medicaid rebate rate substantially;

imposed a significant annual fee on companies that manufacture or import branded prescription drug products and established an annual non-deductible fee on entities that sell branded prescription drugs or biologics to specified government programs in the United States;

expanded the 340B drug discount program (excluding orphan drugs), including the creation of new penalties for non-compliance; and

included a 50% point-of-sale discount off negotiated prices on applicable brand-name drugs for Medicare Part D participants in the coverage gap, or donut hole, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D.

Other legislative and regulatory changes have also been proposed and adopted in the United States since the enactment of the Affordable Care Act. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. These automatic reductions included aggregate reductions of Medicare payments to providers of 2%. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2024 unless additional Congressional action is taken.

In addition, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. Increased scrutiny by the U.S. Congress of the FDA s approval process may subject us to more stringent product labeling and post-marketing testing and other requirements, and delays in feedback from the FDA may affect our ability to update or adjust our label in a timely manner in the interest of patient adherence and tolerability. We cannot predict whether other legislative changes will be adopted or how such changes would affect the pharmaceutical industry generally and the commercialization of PROCYSBI specifically.

Legislative changes regarding manufacturers rebate obligations for new formulations of oral solid dosage form drugs under the Medicaid Drug Rebate Program, if applied to PROCYSBI, would have a material adverse effect on our business, results of operations and financial condition.

The Affordable Care Act created a new formula to determine the rebate amount owed by manufacturers of line extension drugs that may lead to higher rebates owed by such manufacturers under the Medicaid Drug Rebate Program. The Affordable Care Act defined a line extension drug to mean a new formulation of a drug, such as an extended release formulation. In April 2010, CMS stated that it would issue additional guidance to manufacturers and other stakeholders concerning line extensions of existing drugs. In 2012, in implementing the new law, CMS proposed

a broad definition of a line extension drug to include any single source or innovator multiple source drug that is an oral solid dosage form approved by the FDA as a change to the initial brand name listed drug. Examples of line extensions include a new formulation of a previously approved oral solid dosage form drug; a new combination of two or more oral solid dosage form drugs; or a new indication for an already marketed oral solid dosage form drug. In the proposed rule, orphan drugs were not excluded from the definition of a line extension drug. Although CMS has not yet issued a final rule, PROCYSBI may be subject to the new rebate calculations under the Medicaid Drug Rebate Program, causing the rebates payable on Medicaid utilization of PROCYSBI to increase substantially. Approximately 20% of our current PROCYSBI sales by

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volume are to Medicaid beneficiaries. Accordingly, the implementation of the proposed rules may have a material adverse effect on our business, results of operations and financial condition.

We are subject, directly and indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws, corrupt practices and bribery laws and health information privacy and security laws. Failure to comply with these laws may subject us to substantial penalties.

We do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors. However, federal and state healthcare laws and regulations pertaining to fraud and abuse, physician payment transparency, privacy and security laws and regulations may apply to us depending on programs we operate and have been asserted by the government and others to apply to companies like us, and our arrangements with healthcare providers, customers and other entities, including our marketing practices, educational programs and pricing policies. These laws include:

the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs, such as the Medicare and Medicaid programs. The Affordable Care Act amended the federal Anti-Kickback Statute to provide that a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

federal false claims laws, including, without limitation, the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal third-party payors that are false or fraudulent, such as engaging in improper promotion of products or submitting inaccurate price reports to the Medicaid Drug Rebate program;

the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary s decision to order or receive items or services reimbursable by the government from a particular provider or supplier;

federal criminal laws that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters; Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;

the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain

electronic healthcare transactions and protects the security and privacy of protected health information held by certain covered entities and their business associates;

the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children s Health Insurance Program (with certain exceptions) to report annually to CMS information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians described above and their immediate family members and payments or other transfers of value to such physician owners (manufacturers are required to submit reports to CMS by the 90th day of each calendar year);

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in the EEA, in various member states including France, the United Kingdom, the Netherlands, Italy and Spain, rules adopted by the legislator or self-regulatory industry bodies requiring the notification and/or publication of certain transfers of value from pharmaceutical companies to healthcare professionals (for example, France has recently adopted legislation (Law No. 2011-2012, or the French Sunshine Act, and Decree no. 2013-414 which implements it) requiring pharmaceutical companies to disclose and publish agreements with or transfers of value to healthcare professionals);

anti-bribery and anti-corruption laws, such as the U.S. Foreign Corrupt Practices Act (the FCPA), which prohibits corporations and individuals from corruptly paying, offering or promising to pay, or authorizing the payment of anything of value, directly or indirectly, to any foreign government official, political party or party official, or political candidate in an attempt to improperly influence a person working in an official capacity or secure an improper advantage, and which also requires companies to keep accurate books and records and maintain an adequate system of internal accounting controls; the UK Bribery Act, which prohibits both domestic and international bribery, as well as bribery across both public and private sectors; bribery provisions contained in the German Criminal Code, which, pursuant to draft legislation being prepared by the German government, may make the corruption and corruptibility of physicians in private practice and other healthcare professionals a criminal offense; and

analogous state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry s voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. In addition, as we expand our development and commercialization activities outside of the United States, we will need to establish and expand business relationships with various third parties, such as independent contractors, distributors, vendors, consultant, advocacy groups and physicians, and we will interact more frequently with foreign officials, including regulatory authorities and physicians employed by state-run healthcare institutions who may be deemed to be foreign officials under the FCPA, the UK Bribery Act or similar laws of other countries that may govern our activities. Any interactions with any such parties or individuals where compensation or anything of value is provided that are found to be in violation of such laws could result in significant civil and criminal penalties.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under such laws, it is possible that some of our business activities, including our relationships with physicians and other healthcare providers, some of whom recommend, purchase and/or prescribe our products, and the manner in which we promote our products, could be subject to challenge under one or more of such laws. We are also exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. While we have policies and procedures in place prohibiting such activity, misconduct by these parties could include, among other infractions or violations, intentional, reckless and/or negligent conduct or unauthorized activity that violates FDA requirements, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and

abuse laws and regulations, laws that require the true, complete and accurate reporting of financial information or data or other commercial or regulatory laws or requirements. It is not always possible to identify and deter misconduct by our employees and

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other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If our operations are found to violate any of the laws described above or any other laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment of officers involved, any of which could adversely affect our ability to market our current and any future products, once approved, and materially adversely affect our business, results of operations and financial condition. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management s attention from the operation of our business. See also the risk factor titled *If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition*.

Our reliance on third parties may result in delays in completing, or a failure to complete, preclinical testing, clinical trials or regulatory marketing submissions.

In the course of product development, we engage and collaborate with a variety of external organizations to perform services essential to drug product development. The organizations which perform services may include, but are not limited to: governmental agencies and university laboratories; other biotechnology and pharmaceutical companies; CMOs; CROs; distribution and supply (logistics) service organizations; contract testing organizations; consultants or consulting organizations with specialized knowledge based expertise; and intellectual property law firms.

As a result of our engagement of these types of organizations to help us with our product development programs, many important aspects of our business are and will be out of our direct control. Nevertheless, we are responsible for ensuring that each of our product development programs complies with applicable regulatory requirements, and our reliance on these organizations does not relieve us of our regulatory responsibilities. If any such organizations we engage in the future fail to perform their obligations under our agreements with them or fail to perform in a satisfactory manner in compliance with applicable regulatory requirements, we may face delays in completing our development and commercialization processes for any of our drug product candidates and could be required to repeat testing or clinical trials, which would delay the regulatory approval process. Furthermore, any loss or delay in obtaining contracts with such entities may also delay the completion of our clinical trials, regulatory filings and the potential market approval of our drug product candidates.

Specifically, we have and will continue to rely on third parties, such as CROs and/or co-operative groups, to assist us in overseeing and monitoring clinical trials as well as to process the clinical results. Any failure of such third parties to perform or to meet the applicable standards will result in delays in or failures to complete trials. A failure by such third parties to observe the terms of a product development program for any particular product candidate or to complete the clinical trials for a product candidate in the anticipated time frame could materially adversely affect our business, results of operations and financial condition.

In addition, our dependence on collaborative arrangements with third parties subjects us to a number of risks that could harm our ability to develop and commercialize products:

- collaborative arrangements might not be available on terms which are reasonably favorable to us, or at all;

disagreements with partners may result in delays in the development and marketing of products, termination of collaboration agreements or time consuming and expensive legal action;

agreement terms may be difficult or costly to enforce;

partners may not allocate sufficient funds or resources to the development, promotion or marketing of our product candidates, or may not perform their obligations as expected;

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partners may choose to develop, independently or with other companies, alternative products or treatments, including products or treatments which compete with ours;

agreements with partners may expire or be terminated without renewal, or partners may breach agreements with us;

business combinations or significant changes in a partner s business strategy or financial resources might adversely affect that partner s willingness or ability to fulfill its obligations to us; and

the terms and conditions of the relevant agreements may no longer be suitable.

We cannot guarantee that we will be able to negotiate acceptable future collaboration agreements or that those currently in existence will make it possible for us to fulfill our objectives.

We depend on the support of key scientific and medical collaborators.

We must establish and maintain relationships with key opinion leaders, leading scientists and research institutions. We believe that such relationships are critical to establishing products as a standard of care for their approved indications. Although we have various medical and scientific advisors and research collaborations, there is no assurance that our advisors and our research collaborators will continue to work with us or that we will be able to attract additional advisors or collaborators. If we are not able to maintain existing or establish new clinical and scientific relationships to assist in our commercialization and research and development, we may not be able to establish our products as the standard of care or successfully develop our drug product candidates.

If we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results and prevent fraud.

The Sarbanes-Oxley Act of 2002 (the Sarbanes-Oxley Act) requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. During its evaluation of the effectiveness of internal control over financial reporting as of December 31, 2014, management identified a material weakness related to our inventory costing and overhead allocations for our commercial product PROCYSBI and determined that our review of our inventory costing and overhead allocations were not performed at a sufficiently detailed level to detect errors in our inventory and related accounts. With the oversight of management and our Audit Committee, we have initiated actions to address the root causes of the material weakness identified in 2014. There can be no assurance that such actions will be sufficient to remedy the material weakness identified or that additional material weaknesses or other control or significant deficiencies will not be identified in the future. If we continue to experience a material weakness in our internal controls or fail to maintain or implement required new or improved controls, such circumstances could cause us to fail to meet our periodic reporting obligations or result in material misstatements in our financial statements, or adversely affect the results of periodic management evaluations and annual auditor attestation reports. Each of the foregoing results could cause stockholders to lose confidence in our reported financial information and lead to a decline in our stock price.

We may be subject to product liability claims.

The nature of our business exposes us to potential liability risks inherent in the testing (including through human trials), manufacturing and marketing of drugs. Our products and our drug product candidates could potentially harm people, and we may be subject to costly and damaging product liability claims regardless of actual harm. Many of the participants in our clinical trials, cystinosis patients and cystic fibrosis patients are already critically ill or suffering from chronic debilitating diseases. The waivers we obtain from participants in clinical trials may not be enforceable and may not protect us from liability or the costs of product liability litigation.

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The active ingredient in QUINSAIR, levofloxacin, is currently subject to several pending product liability claims. We may have to defend against liability claims related to QUINSAIR or any other of our products in the future. Although we currently carry product liability insurance, it may not be sufficient to cover any claims. We may be unable to maintain product liability insurance in the future at satisfactory rates or in adequate amounts. Regardless of the merits or eventual outcome, product liability claims may result in decreased demand for our product candidates, injury to our reputation, withdrawal of clinical trial participants and inability to continue clinical trials, costs to defend the related litigation, diversion of management s time, substantial monetary awards to trial participants, or patients, regulatory investigations, product recalls or withdrawals, labeling, marketing or promotional restrictions and loss of revenue, any of which may materially adversely affect our business, results or operations and financial condition.

Our success depends on our ability to manage our projected growth.

Our business strategy, including continued commercial sales of PROCYSBI in the United States and certain countries in the EEA, the launch of QUINSAIR in Canada and the EEA, expansion of our commercial operations into other markets, the continuation of our clinical-stage programs and the in-license and acquisition of additional clinical-stage product candidates, will require us to retain existing and add required new qualified and experienced personnel in multiple functional areas over the next several years.

Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to manage the expansion of our operations effectively, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, including additional product candidates.

In addition, in connection with the commercial launch of PROCYSBI in the EEA and the planned launch of QUINSAIR in the EU, we expect to continue to expand our operations and add personnel in Europe. We may encounter difficulties successfully managing remotely a substantially larger and internationally diverse organization and may encounter delays in commercialization if we are not successful in integrating our international operations. Challenges related to managing international operations may arise from staffing and managing foreign operations, reduced or varied protection for intellectual property rights in some countries, potential strain on our financial and managerial controls and reporting systems and procedures, diverse individual country regulatory and statutory laws, the costs of maintaining EEA presence, in-country legal entities and related tax structures, fluctuations in currency exchanges and political and economic instability, including wars, terrorism and political unrest, boycotts, curtailment of trade and other business restrictions.

If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate revenue could be reduced and we may not be able to implement our business strategy.

Credit risks from customers outside the United States may materially adversely affect our business, results of operations and financial condition.

Sales of our products to government supported customers outside of the United States are likely to be subject to significant payment delays due to government funding and reimbursement practices, which will result in an increase in the length of time that we may have accounts receivable outstanding. In addition, many governments in Europe are facing significant liquidity crises. If government reimbursement for sales of our products in EEA countries is delayed or becomes unavailable, we may not be able to collect on amounts payable to us in reasonable time frames from such customers, which would cause our capital requirements to increase and would materially adversely affect our

business, results of operations and financial condition.

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Macroeconomic conditions could materially adversely affect our business, results of operations and financial condition.

Various macroeconomic factors, such as changes in inflation, interest rates, foreign currency exchange rates and overall business and economic conditions and uncertainties, including those resulting from conditions in the global financial markets, could adversely affect our business, results of operations and financial condition. For example, if inflation or other factors were to significantly increase our business costs, it may not be feasible to increase the price of our current or any future products due to reimbursement procedures and other pricing pressures.

In the recent past, the global financial crisis caused financing to be unavailable in many cases or caused the cost of financing to significantly increase. Any similar disruption in the financial markets may increase uncertainty in the debt and equity markets, which may adversely affect our ability to access financing on favorable terms in the future. In addition, our suppliers, manufacturers and other third parties important to our business also may be negatively affected by such potential market dislocations and disruptions, and their businesses may be disrupted, which could materially adversely affect our business, results of operations and financial condition.

Our product sales in the United States could be reduced by imports from countries where our products are available at lower prices.

Our recognized product sales in the United States may be reduced if PROCYSBI is imported into the United States from lower-priced markets, whether legally or illegally. In the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Canada and Mexico. There have been proposals to legalize the import of pharmaceuticals from outside the United States. If such legislation were enacted, our revenues could be reduced, and our business, results of operations and financial condition could be materially adversely affected.

Our international sales and operating expenses are subject to fluctuations in currency exchange rates.

A portion of our business is conducted in currencies other than our reporting currency, the U.S. dollar. We recognize foreign currency gains or losses arising from our operations in the period in which we incur those gains or losses. As a result, currency fluctuations between the U.S. dollar and the currencies in which we do business cause foreign currency translation gains and losses. Because of the number of currencies that may be involved as we enter new markets, the variability of currency exposures and the potential volatility of currency exchange rates, we may suffer significant foreign currency translation and transaction losses due to the effect of exchange rate fluctuations. We have not entered into derivative instruments to offset the impact of foreign exchange fluctuations. Given the volatility of exchange rates, there is no assurance that we will be able to effectively manage currency transaction and/or conversion risks.

We may engage in strategic transactions, in addition to the QUINSAIR acquisition, that could affect our liquidity, increase our expenses and present significant challenges in focus and energy to our management or prove not to be successful.

From time to time, we may also consider additional strategic transactions, such as acquisitions of companies, other asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Pursuant to the asset purchase agreement for the QUINSAIR acquisition, we paid $68.4 million in consideration upon closing of the transaction (subject to certain deductions), approximately $34.2 million of which was paid in shares of our common stock at our election. The transaction consideration also includes contingent payments of up to $350.0 million associated with development, regulatory and commercial milestones, up to $50.0 million of which is payable in our common stock at our election, and a single digit royalty on future global net sales. In addition, we will have

single-digit contingent royalty obligations to two

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additional parties involved in QUINSAIR s development. Additional potential transactions that we may consider include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. The QUINSAIR acquisition and any future transactions could result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could harm our business, financial condition and results of operations. Future acquisitions may also require us to obtain additional financing, which may not be available on favorable terms or at all. Our ability as an organization to integrate acquisitions is relatively unproven. The QUINSAIR acquisition and any future transactions may entail numerous operational and financial risks, including exposure to unknown liabilities; disruption of our business and diversion of our management s time and attention in order to develop acquired products or technologies or to conduct business in new markets; use of existing cash reserves, dilutive issuances of equity securities to replenish cash requirements or to directly pay for transactions, or incurrence of substantial debt to pay for acquisitions; higher-than-expected acquisition and integration costs; increases in near- and long-term expenditures; unexpected difficulties or shortcomings in the development or commercialization of QUINSAIR and any other acquired assets, products or businesses; write-downs of assets or goodwill or impairment charges; increased amortization expenses; difficulty and cost in combining the operations and personnel of any future acquired businesses with our operations and personnel; impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and inability to retain key employees of any acquired businesses. We may not realize the anticipated benefits of the QUINSAIR acquisition or any future transactions.

Accordingly, although we cannot assure you that we will undertake or successfully complete any transactions of the nature described above, the QUINSAIR acquisition and any other future transactions that we do complete may be subject to the foregoing or other risks and could have a material adverse effect on our business, results of operations and financial condition.

Our business involves the use of hazardous materials, and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development activities and those of our third-party manufacturers and suppliers involve the controlled storage, use and disposal of hazardous materials, including components of our product and product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. We do not currently carry biological or hazardous waste insurance coverage. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance.

Significant disruptions of information technology systems or breaches of data security could materially adversely affect our business, results of operations and financial condition.

We are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential

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information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We have also outsourced elements of our information technology infrastructure, and as a result a number of third-party vendors may or could have access to our confidential information. The size and complexity of our information technology systems, and those of third-party vendors with whom we contract, make such systems potentially vulnerable to breakdown, malicious intrusion, security breaches and other cyber-attacks. In addition, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. The costs to us to eliminate or alleviate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business. Despite the extensive measures we may take to secure data and our information technology systems, a determined hacker or other bad actor may still breach these security measures and our information technology systems. Moreover, if a computer security breach affects our systems or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal and state privacy and security laws, if applicable, including the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Clinical Health Act of 2009, and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a risk of loss or litigation and potential liability, which could materially adversely affect our business, results of operations and financial condition.

Business disruptions from the occurrence of a catastrophic disaster could cause damage to our facilities and equipment or that of our third-party manufacturers or suppliers.

Our executive offices and laboratory facility are located in the San Francisco Bay Area near known earthquake fault zones and are vulnerable to significant damage from earthquakes. We and our contract manufacturers and source suppliers of raw materials and critical services are also vulnerable to damage from other types of disasters, including fires, storms and other extreme weather conditions, floods, water shortages, power losses, telecommunications failures, outbreaks of disease and similar events. If such a disaster were to occur, our ability to continue our operations, including commercial sales and product development programs, could be seriously, or potentially completely, impaired. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions, and we may not be able to maintain insurance in the future at satisfactory rates or in adequate amounts.

Risks Related to Intellectual Property and Competition

If we are unable to protect adequately our proprietary technology, we may not be able to compete as effectively, and our business, results of operations and financial condition will be materially adversely affected.

Our success depends significantly on our ability to protect our proprietary technology from unauthorized use by third parties. We will be able to obtain such protection only to the extent our products are covered by valid and enforceable patents or trade secrets. Any non-confidential disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to quickly duplicate or surpass our technological achievements and erode our competitive position in the market. Where we elect to pursue patent protection on our proprietary technology, we file, prosecute and maintain patent applications covering certain aspects of our technology. Patent protection may not be available, however, for some of the drug product candidates we are developing. We are required to spend significant time and money obtaining, maintaining and enforcing our patent rights, designing around patents

held by others and obtaining licenses to third-party patents or other proprietary rights that cover aspects of our product candidates. The patent application process, also

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known as patent prosecution, is expensive and time consuming. It is possible that we or our current licensors, or any future licensors or licensees, may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. If our current licensors, or any future licensors or licensees, are not fully cooperative or disagree with us regarding any aspect of the prosecution, maintenance or enforcement of the patent rights covering our product candidates where they have decision-making rights on such matters, our preferred approach may not be followed and the scope, strength, duration or other aspects of such patent rights could be compromised.

In addition, our patents and applications or those of our licensors may not be prosecuted and enforced in a manner consistent with the best interests of our business. Defects in form in the preparation or filing of our patents or patent applications or those of our licensors may adversely affect proper priority claims, inventorship, claim scope or patent term adjustments. As a result, the patent rights we depend upon to protect our technology may be held invalid or unenforceable or may be limited in scope. Moreover, we cannot assure you that all of the patent applications that we own or license will issue as patents or that, if issued, the claims of such patents will be held valid or enforceable or will have a scope that will be advantageous to us.

The rights granted to us under the issued patents, as well as those that may be granted on pending patent applications that we own or license, may not be of sufficient scope or strength to provide us with any meaningful protection or commercial advantage. In such case, competitors may be able to design around our patents or develop products that provide outcomes comparable to ours without infringing on our intellectual property rights. In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications as a result of the work they performed on our behalf. Although we generally require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to assign or grant similar rights to us under their inventions arising while working for us, we cannot be certain that we have executed such agreements with all who may have contributed to our inventions and intellectual property, nor can we be certain that our agreements with such parties will not be breached.

If any of our patents or those of our licensors are challenged, invalidated or legally circumvented by third parties, and if we do not own other enforceable patents or otherwise have regulatory exclusivity protecting our products, competitors could market products and use processes that are substantially similar to, or superior to, ours, and our business will suffer. Any of these outcomes could impair our ability to succeed against competition from third parties and materially adversely affect our business, results of operations and financial condition.

Our patents, even if issued, may not afford us the degree of protection we require to maintain a competitive advantage.

We own or license issued U.S. and foreign patents and pending U.S. and foreign patent applications related to certain of our drug product candidates and our other technologies. Evaluating the strength of patents covering our products candidates and other technologies in the biopharmaceutical field involves complex legal and scientific questions and can be highly uncertain. While we also rely on orphan drug exclusivity for PROCYSBI for commercial protection, the degree of patent protection we require may be unavailable or severely limited in some cases and may not adequately protect our products or permit us to gain or keep any competitive advantage. For example, the patent applications that we own or license may fail to result in issued patents in the United States or in other countries. Even if patents do issue on such patent applications, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. For example, U.S. patents can be challenged by any person before the U.S. Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB). Patents granted by the European Patent Office may be similarly opposed by any person within nine months from the

publication of the grant. Similar proceedings are available in other jurisdictions, and in the United States, Europe and other jurisdictions, third parties can raise

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questions of validity with a patent office even before a patent has granted. See also the risk factor titled *Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products*.

We recently requested that the FDA remove one of our two patents from the list of patents identified in the FDA Orange Book for PROCYSBI. If a third party such as a generic drug company decided to file an abbreviated new drug application (ANDA) for a generic version of PROCYSBI, that third party would not be required to provide a statement that the specific patent we requested be removed from the FDA Orange Book is invalid or would not be infringed upon by the manufacture, use or sale of the drug product for which the ANDA is submitted (a paragraph IV certification) with respect to that specific patent. However, the third party would be obligated to submit an appropriate certification against the other patent currently listed in the Orange Book for PROCYSBI as well as any additional patents that, if issued, may be listed in the future. While PROCYSBI has received exclusive marketing rights as an orphan drug in the United States into 2020 and therefore has commercial protection on that basis, the FDA can subsequently approve a drug for the same conditions as PROCYSBI under certain circumstances. See also the risk factor titled *If we fail to maintain orphan drug or other regulatory exclusivity for our products or to obtain and maintain exclusivity for our orphan drug product candidates, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.*

Even if they are unchallenged, our patents and patent applications, if granted, may not adequately protect our product candidates or technology or prevent others from designing around our patent claims. For example, a third party may develop a competitive product that provides therapeutic benefits similar to one or more of our product candidates but that falls outside the scope of our patent protection. If the breadth or strength of protection provided by the patents and patent applications we own or license covering our product candidates is successfully challenged, then our ability to commercialize such product candidates could be adversely affected, and we may face unexpected competition that may materially adversely affect our business, results of operations and financial condition.

In addition, competitors may interfere with our success in obtaining and maintaining patent protection for our product candidates and technologies in a variety of ways. Competitors may claim that they invented the claimed invention prior to us or our licensors or may file patent applications before we or our licensors do. For example, because patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we or our licensors were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, for patent applications filed before March 2013 in the United States an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications.

Competitors may also claim that we are infringing on their patents and that we therefore cannot develop or commercialize our product candidates or practice our technology. Competitors may also challenge our patents, if issued, by showing the USPTO or a court that the invention claimed was not novel, was obvious or is not valid for a number of other reasons. If the USPTO or a court agrees, we could lose some or all of our rights to the challenged patents. Competitors may also initiate validity challenges to our patents at the USPTO PTAB. See also the risk factor titled *Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products*.

Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Thus, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Without adequate and continuing patent protection for

our product candidates and technologies, we may be open to competition from generic versions of such products and competitive versions of our technologies.

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If we do not obtain, or if we lose, adequate patent protection for our product candidates, and if we do not have other regulatory exclusivity for such product candidates, others may develop and commercialize products that are the same as, or similar to, our product candidates, which would adversely affect our business, results of operations and financial condition.

We may in the future become involved in lawsuits to defend against third-party allegations of infringement or to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on our business, results of operations and financial condition.

The drug product and biopharmaceutical industry has been characterized by frequent and extensive intellectual property litigation. Our competitors or other third-party patent holders may assert that our products are covered by their patents. Although we believe we have adequate defenses available if faced with any allegations that we infringe third-party patents, we cannot be certain that we do not infringe on those patents or that we will not infringe on patents granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our products. If a patent holder believes our drug product infringes on its patent, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. If our products are found to infringe, we could be prevented from manufacturing or marketing those products.

In addition, competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To stop any such infringement or unauthorized use, litigation may be necessary. If we or one of our licensors were to initiate legal proceedings against a third party to enforce a patent, the defendant could seek to have the patent s validity reviewed through PTAB proceedings or counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements for patent issuance, including lack of novelty, obviousness or enablement. Patents may be unenforceable if someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. The outcomes of proceedings involving assertions of invalidity and unenforceability are unpredictable. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability of our patents covering one of our product candidates or technologies, we would lose at least part, and perhaps all, of the patent protection on such product candidates or technologies. Such a loss of patent protection would materially adversely affect our business, results of operations and financial condition, particularly if we do not have other regulatory protection. Moreover, our competitors could counterclaim in any suit to enforce our patents that we infringe their intellectual property.

Third parties may initiate legal proceedings against us to challenge the validity or scope of our intellectual property rights or may allege an ownership right in our patents resulting from their past employment or consultancy with us. Many of our current and potential competitors have the ability to dedicate substantially greater resources to defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from claiming an ownership interest in or infringing upon or misappropriating our intellectual property. Competing products may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit alleging our infringement of a competitor s patents, we could be prevented from marketing our product candidates in one or more foreign countries.

Litigation related to infringement or misappropriation of a third parties intellectual property rights, with or without merit, is unpredictable, is generally expensive and time consuming and can divert management s attention from our

core business. If we do not prevail in any litigation in which we are alleged to have infringed or misappropriated intellectual property rights, a court could require us to pay substantial damages, treble

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damages and attorneys fees and could prohibit us from using technologies essential to our product candidates, any of which would have a material adverse effect on our business, results of operations and financial condition. If patents asserted against us are upheld as valid and enforceable and we are found to infringe them, we could be prevented from selling our product candidates or technologies unless we can obtain licenses to use the technology or ideas covered by such patents. We do not know whether any necessary licenses would be available to us on satisfactory terms, if at all. If we cannot obtain such licenses, we could be forced to design around the infringed patents at additional cost or to abandon the infringing product candidate or technology altogether. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the market price of our common stock. As a result, our ability to grow our business and compete in the market may be harmed.

We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive rights to technology or product candidates derived from these collaborations. If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while we attempt to design around other patents or even be prohibited from developing, manufacturing or selling drug product candidates requiring these licenses. There is also a risk that disputes may arise as to the rights to technology or drug product candidates developed in collaboration with other parties. Any such disputes may cause our competitive position to be adversely affected and may materially adversely affect our business, results of operations and financial condition.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates or technologies, we may not be able to prevent a competitor from marketing products that are the same as or similar to our products, which would have a material adverse effect on our business, results of operations and financial condition, particularly if we do not have other regulatory protection for our products.

We may not be able to effectively enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our product candidates and technologies in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. In addition, laws of some countries outside of the United States do not afford intellectual property protection to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property

rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual

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property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States. In addition, competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. See also the risk factor titled *Our success depends on our ability to manage our projected growth.*

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, there can be no assurance that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. In addition, our efforts to protect our intellectual property rights in such countries may be inadequate.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on our having valid and enforceable intellectual property rights, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act (the America Invents Act), which became effective on September 16, 2012, could increase those uncertainties and costs. The America Invents Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. For example, the America Invents Act enacted proceedings involving post-issuance patent review procedures conducted before the PTAB, including inter partes review (IPR). The IPR process permits third parties to challenge the validity of a patent on the grounds that it was anticipated or made obvious by prior art, and generic drug manufactures and entities associated with hedge funds have recently begun challenging biopharmaceutical patents with increased frequency based on prior art through the IPR process. Prior art could render our patents or those of our licensors invalid, and the availability of the IPR process as a lower-cost alternative to litigation and faster method for challenging patents could therefore increase the likelihood that our patents or those of our licensors will be challenged and potentially rendered invalid. Moreover, if such challenges occur with respect to our University of California, San Diego (UCSD) licensed patents, UCSD has the right to control the defense of such proceedings.

In addition, the America Invents Act has transformed the U.S. patent system into a first to file system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could materially adversely affect our business, financial condition and results of operations.

The U.S. Supreme Court has ruled on several patent cases in recent years, narrowing the scope of patent protection available in certain circumstances and weakening the rights of patent owners in certain situations. In addition, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if

adopted, could affect our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts,

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the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we are limited in our ability to utilize acquired or licensed technologies, or if we lose our rights to critical in-licensed technology, we may be unable to successfully develop, out-license, market and sell our products, which could prevent or delay new product introductions.

We have acquired and licensed certain proprietary technologies and plan to further license and acquire various patents and proprietary technologies owned by other parties. The agreements in place are critical to our product development programs. For example, most of our patent portfolio pertaining to PROCYSBI and RP103 for cystinosis and other therapeutic indications has been licensed from academic institutions. Our license agreements with these institutions include termination clauses that permit the licensor to terminate our license under certain circumstances, including if we materially breach our obligations under the applicable agreement. If one or more of our licenses is terminated, we would have no further right to use or exploit the patents, know-how and other intellectual property rights licensed to us under the agreement, which could adversely affect our ability to market PROCYSBI or continue our development programs of RP103 in other clinical indications.

In connection with the QUINSAIR acquisition, we entered into a license to certain patent rights held by PARI Pharma GmbH pertaining to customized PARI nebulizer devices for the administration of QUINSAIR. We will be dependent on PARI to maintain these patents and to prosecute any third-party infringement of them. PARI may limit or terminate our rights under this license in the event that we do not fulfill certain diligence obligations. Our business strategy depends on the successful development of licensed and acquired technologies into commercial products. Therefore, any limitations on our ability to utilize these technologies may impair our ability to develop, out-license or market and sell our product candidates, could delay new product introductions and could adversely affect our reputation, any of which could have a material adverse effect on our business, results of operations and financial condition.

If we are unable to protect the confidentiality of our trade secrets, our competitive position may be harmed, and our business, results of operations and financial condition will be materially adversely affected.

In addition to patent protection, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. Our trade secrets may not be adequately protected, however. We have taken steps to protect our trade secrets and proprietary information, including entering into confidentiality agreements and intellectual property assignment agreements with our employees, consultants, advisors and corporate and educational institution partners. Nevertheless, such agreements may not be enforceable or may not provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure, whether willful or unintentional, or other breaches of the agreements, and we may not be able to prevent such unauthorized disclosure. Monitoring unauthorized disclosure is difficult, and we do not know whether the steps we have taken to prevent such disclosure are, or will be, adequate. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that someone illegally obtained and is using our trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets. Our competitors may independently develop equivalent knowledge, methods and know-how. Competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe or misappropriate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

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We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of our competitors or are in breach of non-competition or non-solicitation agreements with our competitors.

We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other proprietary information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may in the future be subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor in breach of their obligations to that employer or competitor. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our products, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. An inability to incorporate such technologies or features would have a material adverse effect on our business, and may prevent us from successfully commercializing our products. In addition, we may lose the right to practice valuable intellectual property rights or personnel as a result of such claims. Moreover, any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent sales representatives. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our products. Any of these events, or a combination thereof, could have a material adverse effect on our business, results of operations and financial condition.

Risks Related to Our Financial Position and Capital Requirements

Our commercial operations and clinical development programs will require substantial future funding which will affect our operational and financial condition.

Our commercial sales program for PROCYSBI, potential commercial program for QUINSAIR and any future approved products and our product development programs will require substantial additional capital, arising from costs incurred to:

- conduct research, preclinical testing and human studies and clinical trials;
- develop and submit regulatory submissions for marketing approvals;
- develop and submit regulatory submissions for marketing approvals;
- establish or contract for pilot scale and commercial scale manufacturing processes and facilities;
- obtain adequate reimbursement for our products;

market and distribute our products; and

establish, develop and maintain quality control, manufacturing, regulatory, medical, distribution, marketing, sales, finance and administrative capabilities to support these programs.

We base our outlook regarding the need for funds on many uncertain variables. Such uncertainties include the success of our commercial sales of PROCYSBI in the United States, the EEA and any additional markets; the success of our efforts to commercialize QUINSAIR and any future approved products; the scope and results of our research initiatives, preclinical testing and human clinical trials; regulatory approvals; the timing of events outside our direct control, such as competing technological and market developments, negotiations with third-party payors and potential strategic partners; and other factors. In addition, certain product programs may require collaborative agreements with corporate partners with greater financial and organizational resources than we have. Such agreements may require substantial time to complete and may not be available in the time frame

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desired or with acceptable financial terms, if at all. Any of these factors may significantly change the timing and amount of our cash requirements as they determine such one-time events as the receipt or payment of milestone-based and other payments.

If we fail to raise additional financing when needed, we may have to delay or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial finance and administrative expenses to sustainable levels, which would have a material adverse effect on our business, results of operating and financial condition.

While we believe that, based on current operating plan assumptions, our cash and cash equivalents will be sufficient to fund operations through at least the second half of 2017, we will need to sell equity or debt securities to raise additional funds to support, among other things, our development and commercialization programs. The sale of additional equity securities or convertible debt securities will result in additional dilution to our stockholders, and newly issued securities may have rights, preferences and privileges senior to those of holders of our common stock. Additional financing may not be available on a timely basis, in amounts or on terms satisfactory to us, or at all. We may be unable to raise additional capital due to a variety of factors, including our financial condition, the status of our research and development programs, the status of regulatory reviews for marketing approvals, the status of our commercialization activities for QUINSAIR and any future approved products, sales of PROCYSBI in existing and additional markets and the general condition of the financial markets. If we fail to raise additional financing when needed, we may have to delay, partner, or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial expenses. If such actions are required, our business, results of operations and financial condition will be adversely affected, and the market value of our common stock may significantly decline.

Our loan agreement with HC Royalty and outstanding convertible senior notes contain a number of restrictive covenants and other provisions, which, if violated, could result in the acceleration of the payment terms of our outstanding indebtedness, which in turn could have a material adverse effect on our business, results of operations and financial condition.

In December 2012, we entered into the Royalty Loan Agreement. Under the HC Royalty Loan Agreement, we agreed to borrow $50.0 million in two $25.0 million tranches. We drew down the first tranche in the amount of $25.0 million in December 2012 and the second tranche of $25.0 million in May 2013 when we achieved the milestone of U.S. approval of PROCYSBI. In July 2014, we entered into an amendment and restatement of the original HC Royalty Loan Agreement and borrowed from HC Royalty a third, $10.0 million tranche under the loan facility. Also in July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers.

The HC Royalty Loan Agreement includes a number of affirmative and negative covenants, including requirements to use commercially reasonable efforts to exploit PROCYSBI and RP103 in specific markets and to comply with applicable laws, and additional restrictions on mergers, sales of assets, the incurrence of liens, the incurrence of additional indebtedness and transactions with our affiliates, among other requirements. The convertible senior notes also include a number of affirmative and negative covenants, including our obligation to offer to repurchase the notes upon a change of control of our company, limitations on the incurrence of additional indebtedness, registration rights for the holders of the notes and other requirements.

The performance of our obligations under the HC Royalty Loan Agreement is secured by our grant of a security interest to HC Royalty in substantially all of our assets and the assets of our domestic subsidiaries and a pledge of stock of certain of our domestic subsidiaries. Our failure to comply with the terms of the HC Royalty Loan

Agreement, the convertible senior notes and related documents could result in an event of default. A change of control of our company, an uncured material adverse effect on our company and certain other specified events could also constitute an event of default under the agreements. In the event of an event of default that is not cured or waived, the payment of all of our indebtedness to HC Royalty and interest thereon and the repayment of the

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convertible senior notes could accelerate. Under the terms of the security agreement, an event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount due than the current balance of our loan.

Any of the events described above, or a combination thereof, could have a material adverse effect on our financial condition and results of operations.

Our cash flows and capital resources may be insufficient to make required payments on our indebtedness.

The required payments of principal and interest on our indebtedness under the HC Royalty Loan Agreement and convertible senior notes may require a substantial portion, or all, of our available cash to be dedicated to the service of these debt obligations. Both the HC Royalty Loan Agreement and the convertible senior notes bear interest at an annual fixed rate of 8.0%. The HC Royalty Loan Agreement also bears a synthetic royalty based on our net revenues from PROCYSBI and other future-approved products in each calendar year. This royalty and the interest under the HC Royalty Loan Agreement and the convertible senior notes are payable quarterly. Principal payments under the HC Royalty Loan Agreement became due beginning in June 2015, and we made a principal payment of $3 million to HC Royalty in June 2015. The convertible senior notes will mature on August 1, 2019, unless earlier converted, redeemed or repurchased.

There can be no assurance that our business will generate sufficient cash flow or that we will have capital resources in an amount sufficient to enable us to pay our indebtedness to HC Royalty or the holders of the convertible senior notes. Our debt obligations may also limit our flexibility to plan for or react to changes in our business and industry and place us at a competitive disadvantage compared to competitors with superior financial resources including less debt. If our cash flows and capital resources are insufficient to fund these debt service obligations, we may be forced to reduce or delay product development, sales and marketing and capital and other expenditures. We may also be forced to restructure our indebtedness or raise additional capital through the issuance of equity or debt instruments, and there can be no assurance that we will be able to refinance any of our indebtedness or raise additional capital on a timely basis, in sufficient amounts, on satisfactory terms or at all. The terms of the HC Royalty Loan Agreement and convertible senior notes may also limit our ability to pursue any of these financing alternatives, and these alternatives nonetheless may not enable us to meet our scheduled debt service obligations.

Failure to meet our debt service obligations may result in an event of default under the HC Royalty Loan Agreement, which would permit the lender to accelerate the payment of all of our indebtedness to HC Royalty and interest thereon. An event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount than the current balance of our loan.

Failure to meet our debt service obligations may also result in an event of default under the convertible senior notes, which would permit the holders to accelerate the payment of the outstanding principal amount of the notes and interest thereon and require us to pay a repayment premium and higher interest. A change of control would also trigger an obligation to repurchase the convertible senior notes.

Any of the events described above, or a combination thereof, could have a material adverse effect on our business, financial condition and results of operations.

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Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, a corporation that undergoes an ownership change is subject to limitations on its ability to utilize its pre-change net operating loss carryforwards to offset future taxable income. Our existing net operating loss carryforwards may be subject to limitations arising from previous ownership changes, and if we undergo an ownership change in the future, our ability to utilize our net operating loss carryforwards could be further limited by Section 382. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change. Furthermore, we may be unable to use a substantial part of our net operating loss carryforwards if we do not attain profitability in an amount sufficient to utilize such losses.

Risks Related to Our Common Stock

Our stock price has been volatile and may continue to be volatile in the future, and our stockholders may not be able to resell shares of our common stock at or above the prices that they paid. The trading volume in our common stock may be relatively low.

Our common stock is quoted on The NASDAQ Global Select Market. The trading price of our common stock has been and may continue to be volatile. During the 52-week period ended September 30, 2015, our average daily trading volume was approximately 1,171,553 shares and the closing sales price per share of our common stock on The NASDAQ Global Select Market ranged from $16.13 to $5.69. Our operating performance, both financial and in the development of approved products, significantly affects the market price of our common stock. A number of factors may affect the market price of our common stock, including:

- the success of our early development work and clinical trials compared to those of others with products similar or related to our products;
- announcements regarding regulatory approvals or approved label indications and patient populations or changes or delays in the regulatory review process;
- unexpected difficulties in commercialization or lower than expected sales;
- lower than expected pricing and reimbursement levels, or no reimbursement at all, for our current and any future products in various markets;
- actions taken by regulatory agencies with respect to our clinical trials, manufacturing supply chain, quality system or sales and marketing activities;
- changes in our relationships with manufacturers, suppliers or collaborators, or our inability to supply enough product to meet demand;

announcements of new products or innovations by us or our competitors and announcements concerning our competitors or our industry in general;

our ability to obtain additional funding;

changes or developments in applicable laws or regulations;

any intellectual property infringement actions in which we may become involved;

sales and profitability;

announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partners or our competitors;

our ability to manage our projected growth;

actual or anticipated fluctuations in our results of operations;

changes in financial estimates or recommendations by securities analysts or their ceasing to publish research or reports about our business;

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- the trading volume of our common stock;
- general economic and market conditions and overall fluctuations in the U.S. equity markets;
- the appeal and current level of investor interest in the biotechnology/biopharmaceutical capital market sector and in companies in general with business, research strategies and product development pipelines which are similar to us; and
- the loss of any of our key scientific or management personnel.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, market launch and commercialization goals, which we sometimes refer to as milestones. These milestones include the completion of reimbursement and pricing negotiations and commercial launches in additional territories, commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. We also prepare estimates of future financial results for planning and budget purposes. From time to time, we may publicly announce the estimated timing of some of these milestones and provide guidance regarding financial results and other metrics. All of these projections will be based on a variety of assumptions. The actual timing of these milestones and actual financial results can vary dramatically compared to our estimates for a number of reasons, including those set forth above, in many cases for reasons beyond our control. If we do not meet the milestones, financial guidance or other expectations as publicly announced or as projected by various security analysts who follow our company, our stockholders or potential stockholders may lose confidence in our ability to meet overall objectives and our financial planning capabilities, and as a result, the market price of our common stock may decline.

In addition, The NASDAQ Global Select Market has, from time to time, experienced extreme price and trading volume fluctuations. The market prices of securities of pharmaceutical, biotechnology and other life sciences companies in a comparable stage to ours historically have been particularly volatile, and trading volume in such securities and our common stock has often been relatively low. Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated or disproportionate to the operating performance of individual companies. During certain periods, the favor of certain industry segments, such as the biotechnology segment, may also be volatile. These changes may affect in particular the market price of our common stock and the stock prices of companies such as ours that do not have conventional measures of financial and business health such as sales, earnings, profitability and related measures. These broad market fluctuations, during which our industry and companies at our stage may experience a stronger degree of market sensitivity, will adversely affect the market price of our common stock. In the past, following periods of volatility in the market resulting in substantial declines in the market price of a company s securities, stockholders have often instituted class action securities litigation against those companies. Such litigation can result in substantial costs and diversion of management attention and resources, which could significantly harm our and reputation and materially adversely affect our business, financial condition and results of operations.

A substantial number of shares of our common stock are eligible for future sale in the public market, and the issuance or sale of equity, convertible or exchangeable securities in the market, including shares issuable upon conversion of our convertible senior notes and shares issuable at our election in satisfaction of payments related to the QUINSAIR acquisition, or the perception of such future sales or issuances, could lead to a decline in the trading price of our common stock.

Any issuance of shares of our common stock or other securities, including for the purposes of raising capital to fund our operations, financing acquisitions and the expansion of our business, will have a dilutive effect on our existing stockholders. In addition, the perceived market risk associated with the possible issuance of a large number of shares of our common stock, including pursuant to the exercise of our currently outstanding stock options, or issuances of securities convertible or exchangeable into a large number of shares of our common stock could cause some of our stockholders to sell their common stock, thus causing the trading price of our common stock to decline. Subsequent sales of our common stock in the open market, exercises of our currently

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outstanding stock options and the subsequent sale of the shares acquired thereunder or the sale by us of shares of our common stock or securities convertible or exchangeable into our common stock for capital raising purposes could also have an adverse effect on the trading price of our common stock. If our common stock price declines, it will be more difficult for us to raise additional capital or we may be unable to raise additional capital at all.

In July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019. The convertible senior notes are convertible at the option of the holder at an initial conversion rate of approximately 57.14 shares of common stock per $1,000 principal amount of convertible senior notes, which is equivalent to an initial conversion price of $17.50, and is subject to adjustment upon certain events and conditions. In addition, we may redeem for cash or require holders to convert the convertible senior notes into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a period of 30 consecutive trading days. The note purchase agreement governing the convertible senior notes provides the holders with registration rights for the shares issued upon conversion of their convertible senior notes subject to certain conditions, and we filed a registration statement to register the resale of the shares of common stock issuable upon conversion of the convertible senior notes. We may be required to pay increased interest on the convertible senior notes if we do not comply with the registration rights provisions of the note purchase agreement. A substantial number of shares of our common stock are reserved for issuance upon conversion of the convertible senior notes. The issuance of shares of our common stock upon conversion of the convertible senior notes would dilute the ownership interest of our common stockholders and may materially adversely affect the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities.

We issued 3,448,001 shares of our common stock as partial consideration at the closing of the QUINSAIR acquisition, including the shares offered for resale by the selling stockholders pursuant to this prospectus. The transaction consideration also includes contingent payments associated with development, regulatory and commercial milestones, up to $50.0 million of which is payable in our common stock at our election. In connection with the QUINSAIR acquisition, we entered into a registration rights agreement with respect to the shares of common stock that may be issued as contingent consideration pursuant to the QUINSAIR asset purchase agreement, in addition to the shares offered pursuant to this prospectus.

In September 2015, we entered into a Sales Agreement with Cowen and Company, LLC (Cowen) to sell shares of our common stock, with aggregate gross sales proceeds of up to $75,000,000, from time to time, through an at the market equity offering program under which Cowen will act as sales agent.

In connection with other collaborations, joint ventures, license agreements or future financings that we may enter into in the future, we may issue additional shares of common stock or other equity securities, and the value of the securities issued may be substantial and create additional dilution to our existing and future common stockholders.

Because we do not intend to pay any cash dividends on our common stock, investors will benefit from an investment in our common stock only if it appreciates in value. Investors seeking dividend income should not purchase shares of our common stock.

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our earnings to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. As a result, the success of an investment in our common stock will depend upon any future appreciation in the value of our common stock. There is no guarantee that our common stock will appreciate in value or even maintain its current price. Investors seeking dividend income should not invest in our common stock.

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Anti-takeover provisions under Delaware law and in our Certificate of Incorporation and Bylaws, as amended, may prevent or complicate attempts by stockholders to change the Board of Directors or current management and could make a third-party acquisition of us difficult.

Our Certificate of Incorporation and Bylaws, as amended, contain provisions that could significantly reduce the value of our shares to a potential acquiror or delay or prevent changes in control or changes in our management without the consent of our Board of Directors. The provisions in our charter documents include the following:

- the right of our Board of Directors to elect a director 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;
- the required approval of at least 66 ⅔% of the shares entitled to vote to remove a director without cause;
- the ability of our Board of Directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences, dividend rights and voting rights, which may be superior to those of the common stock, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror;
- the ability of our Board of Directors to alter our bylaws without obtaining stockholder approval;
- the required approval of at least 66 ⅔% of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;
- the requirement that a special meeting of stockholders may be called only by the Chairman of the Board of Directors, the chief executive officer or the Board of Directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and
- advance notice procedures that stockholders must comply with in order to nominate candidates to our Board of Directors or to propose matters to be acted upon at a stockholders meeting, which may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect the acquiror s own slate of directors or otherwise attempting to obtain control of us.

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the Board of Directors has approved the transaction.

Our Board of Directors may use the provisions described above to prevent changes in the management and control of our company. These provisions could limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions would apply even if we were to receive an offer that some stockholders may consider beneficial. Also, under applicable Delaware law, our Board of Directors may adopt additional anti-takeover measures in the future.

Provisions of the note purchase agreement governing our convertible senior notes may discourage a takeover, which could cause the market price of our common stock to decline.

The repurchase rights and related repurchase premium provided in our convertible senior notes triggered by the occurrence of a change of control may discourage, delay or prevent a third party from acquiring us, even if doing so would benefit our stockholders. In turn, this could cause the market price of our common stock to decline.

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USE OF PROCEEDS

We will not receive any proceeds from the sale of shares by the selling stockholders.

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DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is not complete and may not contain all the information you should consider before investing in our capital stock. This description is summarized from, and qualified in its entirety by reference to, our certificate of incorporation, as amended, and our bylaws, as amended, which have been publicly filed with the SEC. See Where You Can Find More Information; Incorporation by Reference.

Our authorized capital stock consists of:

- 150,000,000 shares of common stock, $0.001 par value; and
- 15,000,000 shares of preferred stock, $0.001 par value.

Common Stock

Dividends

Subject to any preferential rights to receive dividends of any outstanding shares of our preferred stock, the holders of our common stock will be entitled to receive, ratably in proportion to the number of shares of our common stock held by them, any dividends that may be declared on our common stock by our board of directors out of funds legally available for the payment of dividends.

Voting Rights

For the purpose of determining those stockholders entitled to vote at any meeting of our stockholders, except as otherwise provided by law, only persons in whose names shares of stock stand on our stock records on the applicable record date, as provided in our bylaws, as amended, shall be entitled to vote at any meeting of stockholders. Every person entitled to vote shall have the right to do so either in person, by remote communication, if applicable, or by an agent or agents authorized by a proxy granted in accordance with Delaware law. An agent so appointed need not be a stockholder. No proxy shall be voted after three (3) years from its date of creation unless the proxy provides for a longer period.

Each outstanding share of our common stock will entitle the holder to one vote on each matter properly submitted to our stockholders for their vote; provided, however, that holders of our common stock shall not be entitled to vote on any amendment to our certificate of incorporation, as amended, that relates solely to the terms of one or more outstanding series of our preferred stock if the holders of such affected series of preferred stock are entitled to vote thereon. The holders of our common stock are not entitled to cumulative voting rights in the election of our directors, which means that holders of a majority of the outstanding shares of our common stock will be entitled to elect all of our directors standing for election by holders of our common stock.

Our bylaws, as amended, provide that our stockholders have the power to adopt, amend or repeal our bylaws; provided, that in addition to any vote of the holders of any class or series of our stock required by law or by our certificate of incorporation, as amended, such action by stockholders shall require the affirmative vote of the holders of at least 66 ⅔% of the voting power of all of the then-outstanding shares of our capital stock entitled to vote generally in the election of directors, voting together as a single class. Our board of directors also is empowered to amend our bylaws without the consent of our stockholders. In addition, our certificate of incorporation, as amended,

and our bylaws, as amended, provide that a director may be removed at any time (a) with cause by the affirmative vote of the holders of a majority of the voting power of all then-outstanding shares of our capital stock entitled to vote at an election of directors or (b) without cause by the affirmative vote of the holders of 66 ⅔% of the voting power of all then-outstanding shares of our capital stock entitled to vote at an election of directors.

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No Preemptive or Similar Rights

Our common stock is not entitled to preemptive or similar rights to acquire shares of our common stock or other securities and is not subject to conversion into other securities or redemption at our option or at the option of any holder.

Right to Receive Liquidation Distributions

If we voluntarily or involuntarily liquidate, dissolve or wind-up, the holders of our common stock will be entitled to receive, after payment of or provision for all of our debts and other liabilities and distribution in full of the preferential amounts, if any, to be distributed to the holders of any outstanding preferred stock, all of our remaining assets available for distribution, ratably in proportion to the number of shares of our common stock held by them.

Other

Our outstanding common stock is fully paid and non-assessable. The rights, preferences and privileges of holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of our preferred stock, which our board of directors may designate and issue in the future.

Transfer Agent

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

Preferred Stock

Our board of directors is authorized, without action by our stockholders, to provide for the issuance of shares of preferred stock in one or more series, and to fix the number of shares and to determine for each series such voting rights, if any, designations, preferences and relative, participating, optional or other rights and such qualifications, limitations or restrictions as provided in a resolution or resolutions adopted by our board of directors. Prior to the issuance of shares of a series of preferred stock, we are required by the General Corporation Law of the State of Delaware, or the DGCL, to file a certificate of designation with the Secretary of State of the State of Delaware. The certificate of designation sets forth, for each such series, the designations, powers, preferences, rights, qualifications, limitations and restrictions, established by the resolution or resolutions of our board of directors as described above.

Our board of directors, without stockholder approval, could issue one or more series of our preferred stock with voting, economic or other rights that are senior or superior to those of our common stock that could, among other things, dilute the voting power of our common stock, reduce the likelihood that holders of our common stock will receive dividend payments (if we were to elect to pay dividends) or payments in the event of our liquidation, dissolution or winding-up, and delay, deter or prevent a change in control or other takeover of our company.

Anti-Takeover Effects of Delaware Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. Under Section 203, we are generally prohibited, subject to certain exceptions, from engaging in any business combination with any interested stockholder (as those terms are defined in Section 203) for a period of three years following the time that this stockholder became an interested stockholder unless:

prior to this time, our board of directors approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

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upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of our voting stock outstanding at the time the transaction commenced, excluding shares owned by persons who are our directors and also officers and by 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

at or subsequent to such time, the business combination is approved by our board of directors and authorized at an annual or special meeting of our stockholders, and not by written consent, by the affirmative vote of at least 66 ⅔% of the outstanding voting stock that is not owned by the interested stockholder.

Under Section 203, a business combination includes in general, with respect to a Delaware corporation such as us:

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

any sale, transfer, pledge or other disposition to or with the interested stockholder of assets of the corporation with an aggregate market value equal to or greater than 10% of either the aggregate market value of the corporation s consolidated assets or the aggregate market value of the corporation s outstanding stock;

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

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of 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 loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder, subject to exceptions, as (a) an entity or person beneficially owning, or within three years prior to the determination of interested stockholder status that did own, 15% or more of the outstanding voting stock of the corporation and (b) any affiliate or associate (as those terms are defined in Section 203) of the corporation that was the owner of 15% or more of the outstanding voting stock of the corporation within the prior three years, and affiliates and associates of any of the foregoing persons.

The foregoing description of some of the terms of Section 203 of the Delaware General Corporation Law is not complete and is qualified by reference to Section 203.

Anti-Takeover Effects of Our Certificate of Incorporation and Bylaws

Certain provisions of our certificate of incorporation, as amended, and bylaws, as amended, as well as the provisions of Section 203 of the Delaware General Corporation Law described above, could have the effect of delaying, deterring or preventing another party from acquiring or seeking to acquire control of us. These provisions are intended to discourage certain types of coercive takeover practices and inadequate takeover bids and to encourage anyone seeking to acquire control of us to negotiate first with our board of directors. However, these provisions may also delay, deter

or prevent a change in control or other takeover of our company that our stockholders might consider to be in their best interests, including transactions that might result in a premium being paid over the market price of our common stock and also may limit the price that investors are willing to pay in the future for our common stock. These provisions may also have the effect of preventing changes in our management.

Our certificate of incorporation, as amended, and bylaws, as amended, include anti-takeover provisions that:

- authorize our board of directors, without further action by the stockholders, to issue preferred stock in one or more series and, with respect to each series, to fix the number of shares constituting that series and to establish the rights and other terms of that series, which may include dividend and liquidation rights and preferences, conversion rights and voting rights;

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provide that the number of directors that shall constitute our board of directors shall be fixed exclusively by resolutions adopted by our board of directors and that vacancies on our board of directors, including newly created directorships resulting from any increase in the number of our directors, shall, unless otherwise determined by our board of directors or required by law, be filled only by the affirmative vote of a majority of our directors then in office, even though less than a quorum, and not by our stockholders;

require that actions to be taken by our stockholders may only be taken at an annual or special meeting of our stockholders and not by written consent;

specify that special meetings of our stockholders can be called only by the Chairman of our board of directors, our Chief Executive Officer, our President or our board of directors and not by our stockholders or any other persons;

establish advance notice procedures for stockholders to submit nominations of candidates for election to our board of directors and other proposals to be brought before a stockholders meeting;

require the affirmative vote of the holders of at least 66 ⅔% of the voting power of all of our then-outstanding shares of capital stock entitled to vote generally at an election of directors in order to remove the board of directors or any individual director without cause;

provide that both our board of directors and our stockholders may adopt, amend or repeal our bylaws, provided that, in addition to any vote of any class or series of stock required by law or our certificate of incorporation, as amended, the affirmative vote of the holders of 66 ⅔% of the voting power of all then-outstanding shares of our capital stock entitled to vote generally in the election of directors shall be required for our stockholders to adopt, amend or repeal any provision of our bylaws; and

do not give the holders of our common stock cumulative voting rights with respect to the election of directors, which means that the holders of a majority of our outstanding shares of common stock can elect all directors standing for election by the holders of our common stock.

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SELLING STOCKHOLDERS

On October 2, 2015, we entered into an Amended and Restated Asset Purchase Agreement (the Purchase Agreement) with our wholly owned subsidiary, Raptor Pharmaceuticals Inc., and Tripex, providing for the purchase from Tripex of various assets and rights related to levofloxacin solution for inhalation, a pharmaceutical product also known as Aeroquin, MP-376 and Quinsair (the Asset Purchase). At the closing of the Asset Purchase on October 2, 2015, we issued to Tripex as partial consideration for the assets acquired 3,448,001 shares of our common stock (the Registrable Securities), which shares were subsequently distributed by Tripex to certain of its members (the selling stockholders).

On August 20, 2015, we entered into a registration rights agreement with Tripex and the selling stockholders, pursuant to which we agreed to file with the SEC a registration statement on Form S-3 registering the resale of the Registrable Securities by the selling stockholders and to file additional registration statements on Form S-3 to register the resale of any additional shares of common stock that may be issued in the future by us at our election as contingent consideration pursuant to the Purchase Agreement.

The following table sets forth information with respect to the shares beneficially owned by the selling stockholders. The information regarding shares owned after the offering assumes the sale of all shares offered by the selling stockholders.

Information about the selling stockholders may change over time. Any changed or new information given to us by the selling stockholders will be set forth in supplements to this prospectus or amendments to the registration statement of which this prospectus is a part, if and when necessary.

Except for the transactions referred to herein and in documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, none of the selling stockholders has, or within the last three years has had, any position, office or other material relationship (legal or otherwise) with us or any of our subsidiaries other than as a holder of our securities.

The selling stockholders may sell all, some or none of their shares in this offering. See Plan of Distribution.

Name of Selling Stockholder	Number of Shares of Common Stock Owned Prior to Offering	Maximum Number of Shares of Common Stock to be Sold Pursuant to this Prospectus	Number of Shares of Common Stock Owned After Offering
Aberdare Partners III, L.P. (1)	14,827	14,827	0
Aberdare Ventures III, L.P. (1)	630,981	630,981	0
Adams Street V, L.P. (2)	253,117	253,117	0
HBM Mpex Holding Ltd. (3)	799,319	799,319	0
Investor Group, L.P. (4)	195,996	195,996	0
Investor Growth Capital Limited (5)	457,324	457,324	0
RiverVest Venture Fund II (Ohio), L.P. (6)	44,494	44,494	0

RiverVest Venture Fund II, L.P. (7)	163,811	163,811	0
SV Life Sciences Fund IV Strategic Partners, L.P. (8)	7,983	7,983	0
SV Life Sciences Fund IV, L.P. (9)	281,192	281,192	0
International Life Sciences Fund III (LP1), L.P. (10)	586,397	586,397	0
International Life Sciences Fund III Co-Investment, L.P. (11)	6,958	6,958	0
International Life Sciences Fund III Strategic Partners, L.P. (12)	5,602	5,602	0

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(1) Aberdare GP III, LLC (the Aberdare GP) serves as the general partner of Aberdare Ventures III, L.P. and Aberdare Partners III, L.P. (collectively, Aberdare Fund III) with a total of 645,808 shares of Company common stock. The Aberdare GP has the voting and investment control of the 645,808 shares owned by Aberdare Fund III and may deem to be the beneficial owner of such shares.

Paul H. Klingenstein is a manager in the Aberdare GP who shares voting and investment power with other managers. Paul disclaims ownership of Company shares except to his pecuniary interest in Aberdare Fund III.

(2) Adams Street V, L.P., is the record owner of 253,117 shares of Company common stock (the Adams Shares). The Adams Shares owned by Adams Street V, L.P. may be deemed to be beneficially owned by Adams Street Partners, LLC, the general partner of Adams Street V, L.P. David Brett, Jeffrey T. Diehl, Elisha P. Gould III, Robin P. Murray, Sachin Tulyani, Craig D. Waslin and David S. Welsh, each of whom is a partner of Adams Street Partners, LLC (or a subsidiary thereof) may be deemed to have shared voting and investment powers over the Adams Shares. Adams Street Partners, LLC and David Brett, Jeffrey T. Diehl, Elisha P. Gould III, Robin P. Murray, Sachin Tulyani, Craig D. Waslin and David S. Welsh disclaim beneficial ownership of the Adams Shares except to the extent of their pecuniary interest therein.

(3) HBM Mpex Holding Ltd. is owned by the following entities in the proportions indicated: HBM Healthcare Investments (Cayman) Ltd. 50%, HBM BioCapital (EUR) L.P. 37.40% and HBM BioCapital (USD) L.P. 12.60%. The Sole Director of HBM Mpex Holding Ltd. is Jean-Marc Lesieur. Voting and investment power over the shares ultimately held by HBM Healthcare Investments (Cayman) Ltd. is exercised by the board of directors of HBM Healthcare Investments (Cayman) Ltd. The board of directors of HBM Healthcare Investments (Cayman) Ltd. consists of Jean-Marc Lesieur, Sophia Harris, Richard Coles, Dr. Andreas Wicki, Paul Woodhouse and John Urquhart, none of whom has individual voting or investment power with respect to the shares. Voting and investment power over the shares ultimately held by HBM BioCapital (USD) L.P. and HBM BioCapital (EUR) L.P., respectively, is exercised by its general partner, HBM BioCapital Ltd. The board of directors of HBM BioCapital Ltd. consists of Jean-Marc Lesieur and Dr. Andreas Wicki, none of whom have individual voting or investment power with respect to the shares.

(4) Investor Growth Capital LLC, Delaware limited liability company (the IGC GP) is the general partner of Investor Group L.P. The IGC GP possesses the sole power to direct the disposition of all securities of the Company held by Investor Group L.P. The IGC GP is controlled by a Board of Directors consisting of Michael V. Oporto, Noah Walley and Lennart Johansson. Messrs. Oporto and Walley are citizens of the United States of America; Mr. Johansson is a citizen of the Kingdom of Sweden.

(5) Investor Growth Capital Limited, a Cayman limited liability company (IGCL), possesses sole power to vote and direct the disposition of all securities of the Company held by IGCL. IGCL is controlled by a Board of Directors consisting of Michael V. Oporto, Noah Walley and Lennart Johansson. Messrs. Oporto and Walley are citizens of the United States of America; Mr. Johansson is a citizen of the Kingdom of Sweden.

(6) John P. McKeam, Ph.D. is an authorized person and Thomas C. Melzer and Jay Schmelter are members of RiverVest Venture Partners II, LLC, the general partner of RiverVest Venture Partners II, L.P. RiverVest Venture Partners II, L.P. is the sole member of RiverVest Venture Partners II (Ohio), LLC, which is the general partner of RiverVest Venture Fund II (Ohio), L.P. As an authorized person or member, as the case may be, of RiverVest Venture Partners II, LLC, Dr. McKearn and Messrs. Melzer and Schmelter may be deemed to share dispositive voting and investment power with respect to the shares held by RiverVest Venture Fund II (Ohio), L.P. Dr. McKearn and Messrs. Melzer and Schmelter disclaim beneficial ownership of such shares except to the extent of their pecuniary interest therein.

(7) John P. McKearn, Ph.D. is an authorized person and Thomas C. Melzer and Jay Schmelter are members of RiverVest Venture Partners II, LLC, the general partner of RiverVest Venture Partners II, L.P., which is the general partner of RiverVest Venture Fund II, L.P. As an authorized person or member, as the case may be, of

RiverVest Venture Partners II, LLC, Dr. McKearn and Messrs. Melzer and Schmelter may be deemed to share dispositive voting and investment power with respect to the shares held by RiverVest Venture Fund II, LP. Dr. McKearn and Messrs. Melzer and Schmelter disclaim beneficial ownership of such shares except to the extent of their pecuniary interest therein.

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(8) SV Life Sciences Fund IV (GP), L.P. is the General Partner of SV Life Sciences Fund IV Strategic Partners, L.P. SVLSF IV, LLC is the General Partner of SV Life Sciences Fund IV (GP), L.P. The Investment Committee of SVLSF IV, LLC is comprised of the following individuals: James Garvey, Eugene D. Hill, III, Kate Bingham, David Milne and Michael Ross.

(9) SV Life Sciences Fund IV (GP), L.P. is the General Partner of SV Life Sciences Fund IV, L.P. SVLSF IV, LLC is the General Partner of SV Life Sciences Fund IV (GP), L.P. The Investment Committee of SVLSF IV, LLC is comprised of the following individuals: James Garvey, Eugene D. Hill, III, Kate Bingham, David Milne and Michael Ross.

(10) International Life Sciences Fund III (GP), L.P. is the General Partner of International Life Sciences Fund III (LPl), L.P. ILSF III, LLC is the General Partner of International Life Sciences Fund III (GP), L.P. The Investment Committee of ILSF III, LLC consists of the following individuals: James Garvey, Eugene D. Hill, III, Kate Bingham and Michael Ross.

(11) International Life Sciences Fund III (GP), L.P. is the General Partner of International Life Sciences Fund III Co-Investment, L.P. ILSF III, LLC is the General Partner of International Life Sciences Fund III (GP), L.P. The Investment Committee of ILSF III, LLC consists of the following individuals: James Garvey, Eugene D. Hill, III, Kate Bingham and Michael Ross.

(12) International Life Sciences Fund III (GP), L.P. is the General Partner of International Life Sciences Fund III Strategic Partners, L.P. ILSF III, LLC is the General Partner of International Life Sciences Fund III (GP), L.P. The Investment Committee of ILSF III, LLC consists of the following individuals: James Garvey, Eugene D. Hill, III, Kate Bingham and Michael Ross.

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PLAN OF DISTRIBUTION

The selling stockholders and any of their pledgees, donees, transferees, assignees or other successors-in-interest may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of our common stock or interests in shares of our common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale or at negotiated prices. The selling stockholders may use one or more of the following methods when disposing of the shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- through brokers, dealers or underwriters that may act solely as agents;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- through the writing or settlement of options or other hedging transactions entered into after the effective date of the registration statement of which this prospectus is a part, whether through an options exchange or otherwise;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- a combination of any such methods of disposition; and
- any other method permitted pursuant to applicable law.

The selling stockholders may also sell shares under Rule 144 under the Securities Act, if available, rather than under this prospectus.

Broker-dealers engaged by the selling stockholders may arrange for other broker-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the selling stockholders (or, if any broker-dealer acts as

agent for the purchaser of shares, from the purchaser) in amounts to be negotiated. The selling stockholders do not expect these commissions and discounts to exceed what is customary in the types of transactions involved.

The selling stockholders may from time to time pledge or grant a security interest in some or all of the shares of our common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell shares of our common stock from time to time under this prospectus, or under a supplement or amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus.

Upon being notified in writing by a selling stockholder that any material arrangement has been entered into with a broker-dealer for the sale of our common stock through a block trade, special offering, exchange distribution or secondary distribution or a purchase by a broker or dealer, we will file a supplement to this prospectus, if required, pursuant to Rule 424(b) under the Securities Act, disclosing (i) the name of each such selling stockholder and of the participating broker-dealer(s), (ii) the number of shares involved, (iii) the price at which such shares of our common stock were sold, (iv) the commissions paid or discounts or concessions allowed to such broker-dealer(s), where applicable, (v) that such broker-dealer(s) did not conduct any

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investigation to verify the information set out or incorporated by reference in this prospectus, and (vi) other facts material to the transaction. In addition, upon being notified in writing by a selling stockholder that a donee or pledge intends to sell more than 500 shares of our common stock, we will file a supplement to this prospectus if then required in accordance with applicable securities law.

The selling stockholders also may transfer the shares of our common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of the shares of our common stock or interests in shares of our common stock, the selling stockholders may enter into hedging transactions after the effective date of the registration statement of which this prospectus is a part with broker-dealers or other financial institutions, which may in turn engage in short sales of our common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short after the effective date of the registration statement of which this prospectus is a part and deliver these securities to close out their short positions, or loan or pledge our common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions after the effective date of the registration statement of which this prospectus is a part with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The selling stockholders and any broker-dealers or agents that are involved in selling the shares may be deemed to be underwriters within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act.

We have advised the selling stockholders that they are required to comply with Regulation M promulgated under the Securities Exchange Act of 1934, as amended, during such time as they may be engaged in a distribution of the shares. The foregoing may affect the marketability of our common stock.

The aggregate proceeds to the selling stockholders from the sale of our common stock offered by them will be the purchase price of our common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of our common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

We are required to pay all fees and expenses incident to the registration of the shares. We have agreed to indemnify the selling stockholders against certain losses, claims, damages, liabilities and expenses (including reasonable attorneys fees), including liabilities under the Securities Act or any other statute or at common law.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus constitutes a part effective until the earlier of (a) one hundred eighty (180) days following the effective date thereof and (b) until the selling security holders have completed the distribution described in this registration statement.

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MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of our common stock sold by selling securityholders pursuant to this prospectus, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or non-U.S. tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended (the Code), Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service (the IRS), in each case in effect as of the date hereof. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder of our common stock. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to that discussed below regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that 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 U.S. federal income tax consequences relevant to a Non-U.S. Holder s particular circumstances, including the impact of the Medicare contribution tax on net investment income. In addition, it does not address consequences relevant to Non-U.S. Holders subject to special rules, including, without limitation:

U.S. expatriates and former citizens or long-term residents of the United States;

persons subject to the alternative minimum tax;

persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;

banks, insurance companies, and other financial institutions;

brokers, dealers or traders in securities;

controlled foreign corporations, passive foreign investment companies, and corporations that accumulate earnings to avoid U.S. federal income tax;

partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);

tax-exempt organizations or governmental organizations;

persons deemed to sell our common stock under the constructive sale provisions of the Code;

persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and

tax-qualified retirement plans.

If an entity treated as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATIONAL PURPOSES ONLY AND IS NOT TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND

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DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a Non-U.S. Holder is any beneficial owner of our common stock that is neither a U.S. person nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

an individual who is a citizen or resident of the United States;

a corporation 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 U.S. federal income tax regardless of its source; or