Raptor Pharmaceutical Corp
Form 10-K
March 17, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

[X] ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2013

[ ] TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number 000-50720

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.)

5 Hamilton Landing, Suite 160, Novato, CA 94949
(Address of principal executive offices) (Zip Code)

(415) 408-6200
(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.001 par value	The NASDAQ Global Market
Preferred Share Purchase Rights	

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes [X] No [ ]
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes [ ] No [X]

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes [X] No [ ]

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. [X]

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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 [ ] Accelerated filer [X] Non-accelerated filer [ ] (Do not check if a smaller reporting company) Smaller reporting company [ ]

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2013 (the last business day of the registrant's most recently completed second quarter) was $536.4 million.

Indicate the number of shares outstanding of each of the registrant's classes of common stock, as of the latest practicable date: 62,479,286 shares common stock, par value $0.001, outstanding as of February 28, 2014.

The documents incorporated by reference are as follows:

None.

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RAPTOR PHARMACEUTICAL CORP.

2013 Form 10-K Annual Report

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FORWARD-LOOKING STATEMENTS

Change in Fiscal Year End

On December 4, 2012, the board of directors of Raptor Pharmaceutical Corp., or the "Company", approved a change to the Company's fiscal year end from August 31 to December 31. This Annual Report on Form 10-K includes the financial information for 2013 which refers to the period from January 1 to December 31, 2013. The Company previously filed a report on Form 10-K/T, as amended, for the four-month period from September 1, 2012 to December 31, 2012, or the Transition Period. References in this Annual Report on Form 10-K to fiscal years prior to 2013 refer to the period from September 1 through August 31 of such year.

Forward-Looking Statement

In this Annual Report on Form 10-K, in our other filings with the Securities and Exchange Commission, or 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, 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," "continues," "estimates," "potential," "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 of 1933, as amended, or 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 titled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K 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 Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events or for any other reason.

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PART I

ITEM 1: BUSINESS

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2013, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Unless otherwise stated or the context requires otherwise, for the period from and after the effective time of the 2009 Merger (as described below under "Corporate Information"), all references in this Annual Report on Form 10-K to the "Company," "we," "our," "us," "Raptor" and similar references refer to the company formerly known as TorreyPines Therapeutics, Inc. and now known as Raptor Pharmaceutical Corp. and its direct and indirect wholly-owned subsidiaries Raptor Pharmaceuticals Inc., or Raptor Pharmaceuticals, Raptor European Products, LLC, RPTP European Holdings C.V., Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS and Raptor Pharmaceuticals Germany GmbH.

Overview

We are a biopharmaceutical company focused on developing and commercializing life-altering therapeutics that treat debilitating and often fatal diseases.

Our first product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, or PROCYSBI, received marketing approval from the U.S. Food and Drug Administration, or FDA, on April 30, 2013 for the management of nephropathic cystinosis in adults and children six years and older. On September 6, 2013, the European equivalent, PROCYSBI gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received a Community or EU marketing authorization from the European Commission, or EC, as an orphan medicinal product for the management of proven nephropathic cystinosis. 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 years and 10 years of market exclusivity as an orphan drug in the U.S. and the EU, respectively. We commenced commercial sales of PROCYSBI in the U.S. in June 2013 and plan to launch PROCYSBI in the EU in the first half of 2014.

As of December 31, 2013, 165 U.S. commercial patients were taking PROCYSBI at a Wholesale Acquisition Cost, or WAC, price for PROCYSBI of $15,562.50 per bottle of 250 75-mg capsules and $3,735.00 per bottle of 60 25-mg capsules, resulting in an estimated average annualized price of $250,000 per patient in the U.S. In September 2013, we executed an agreement to participate in the U.S. State Medicare/Medicaid rebate program, which will be reflected in our net revenues in mandatory rebates on reimbursements for patients receiving state Medicaid insurance coverage.

Cysteamine Mechanism of Action

Cysteamine, or 2-aminoethanethiol, is a highly-reactive molecule generated in the cell during the metabolism of cysteine. Cysteamine is used to construct the key enzymatic cofactor involved in energy produced from sugars and lipids. Cysteamine's uniquely reactive properties result in many physiological effects when given exogenously in pharmaceutical doses.

- Antioxidation – Cysteamine is known to increase levels of a key cellular antioxidant, glutathione. Glutathione is composed of the amino acids gamma-glutamate, cysteine and glycine. The availability of cysteine is the major rate-limiting factor in glutathione production. Cysteamine may release cysteine in the circulation, or from within the cell. Cysteamine has been shown to activate the NRF2 pathway, which leads to the increased expression of a wide variety of proteins involved in antioxidant which may help to reduce oxidative stress in CNS and mitochondrial disorders..

- Heat shock response induction – Heat shock proteins, or HSPs, are chaperones that play an important role in protein-protein interactions such as folding and assisting in the establishment of proper protein conformation. Proper protein folding may also prevent unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell. HSPs are typically produced by the cell in response to stress or injury, or other metabolic imbalance. HSPs are part of a cell's mechanism for protein

maintenance. The presence of cysteamine within a cell has been shown to increase transcription of certain HSPs that are key components to the cell's ability to maintain the integrity of proteins.

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- Anti-fibrosis – Cysteamine inhibits formation of three cross-links in collagen that exacerbate fibrotic pathology:
  - gamma-glutamyl peptide bonds, formed by transglutaminase
  - oxidized lysyl-lysine conjugates, formed by lysyl oxidase
  - inter-chain disulfide bonds

Cysteamine also inhibits transcription of a variety of collagens and basement membrane-related proteins.

- Metal chelation – In vitro studies have shown that cysteamine chelates metals, including copper, zinc and iron. High doses of cysteamine can lead to copper depletion, implying that chelation effects also occur in vivo.

- Induction of DNA repair mechanisms – Cysteamine, for over sixty years, has been known to mitigate the effects of radiation.

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 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.

About Nephropathic Cystinosis

There are an estimated 500 patients reported with cystinosis living in the U.S. and 2,000 worldwide. Nephropathic cystinosis comprises 95% of known cases of cystinosis. Elevated cystine leads to cellular dysfunction and death. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children present with symptoms including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy. Untreated, the disease is usually fatal by the end of the first decade of life.

Cystine depletion is the only approved treatment for nephropathic cystinosis. Committed adherence and persistence to cystine depletion therapy is critical to achieve optimal clinical outcomes. Failure to adhere to prescribed dosing of cystine depletion therapy results in poor symptomatic control as cystine accumulates intracellularly and patients consequently experience disease progression, including kidney insufficiency leading to dialysis and kidney transplantation, muscle wasting and in most cases, premature death. Even brief interruptions in daily therapy can permit toxic accumulation of cystine, exposing tissues to renewed, progressive deterioration.

In October 2013, we executed a collaboration agreement with DaVita Clinical Research to screen blood samples from U.S. patients with end-stage renal disease in an effort to identify patients with unrecognized late-onset nephropathic cystinosis.

RP103 Clinical Development

Huntington's Disease

Huntington's disease, or HD, formerly called Huntington's chorea, is a rare, inherited neurodegenerative disorder. 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: chorea (jerky movements), neuropsychiatric symptoms, loss of executive functioning and dementia. HD is caused by an autosomal dominant mutation in a gene called huntingtin, which means any child of an affected person typically has a 50% chance of inheriting the disease. The huntingtin gene encodes a protein that is also called "huntingtin." Expansion of a CAG triplet repeat within the huntingtin gene results in a mutant form of the protein, which gradually damages cells in the brain. HD manifests as a triad of movement, cognitive and psychiatric symptoms which progress gradually in

severity over 15-20 years, eventually causing severe physical and mental disability and potentially early death. The symptoms of HD usually become evident between the 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 (with tetrabenazine, XENAZINE®, approved by FDA) and mood swings associated with HD as well as a variety of physical, occupational and dietary therapies.

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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, or CHU, d'Angers, France, 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, or TMS, of the Unified Huntington's Disease Rating Scale, or 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, Score ≥ 5, Total Functional Capacity, or TFC, > 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.

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 randomized in the study based on concomitant medications. 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 total motor score of 2.84 points of progression in the RP103 treatment arm versus 6.78 for the placebo group (p= 0.03). The lower change of the TMS score for patients treated with RP103 represents a clinically significant slower rate of decline of more than 50% compared to those patients receiving placebo.

There were no new or unusual variations from RP103's clinical safety profile with 48 of 52 patients experiencing at least one adverse event, or 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), mostly nausea, vomiting, abdominal pain, constipation, headache and breath odor. There were five patients treated with RP103 who experienced serious adverse events, or 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 serious adverse events including one for lymphopenia, one for repetitive faintness and one for elevated liver enzymes. One SAE in the placebo group, anxiety, resulted in discontinuation.

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 plan to apply for orphan drug designation in the EU with these topline results.

RP103 Mechanism in HD

In HD, mutant Htt aggregate formation and processing leads to neuronal, mitochondrial and cellular dysfunction and death. Cysteamine may induce several beneficial stress responses, including the production of glutathione, that in aggregate reduce cellular oxidative stress. Through inhibition of several intracellular enzymes, such as transglutaminase, cysteamine inhibits protein aggregation, which are known to form in HD. Cysteamine also increases transcription and production of certain heat shock proteins, which may assist in clearing or repairing misfolded Htt and other proteins in neuronal cells. Cysteamine and its dimer cystamine have been shown in preclinical studies to increase levels of brain derived neurotropic factor, or BDNF, by assisting in the excretion and production of the protein. BDNF is induced by cortical neurons and helps support survival, growth and differentiation

of new neurons and synapses. Two master genes, huntingtin, or Htt, and huntingtin-associated protein, or Hap1, govern BDNF axonal transport and secretion. Expression of the Bdnf gene is reduced in both Alzheimer's and Huntington's disease patients and HD patients are believed to be deficient in BDNF. The Bdnf gene may play a role in the regulation of stress response and in the biology of mood disorders. Finally, cysteamine's metal-chelating properties may assist in removing excess copper, a metal that has shown increased accumulation in brains of people with HD as well as other neurodegenerative disorders.

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Non-alcoholic Fatty Liver Disease in Children

Non-alcoholic fatty liver disease, or NAFLD, is the hepatic component of metabolic syndrome and is associated with deposition of triglycerides in the hepatocytes in individuals who do not consume alcohol in amounts generally considered to be harmful to the liver. NAFLD is commonly associated with elements of metabolic syndrome, such as obesity, diabetes mellitus and hypertriglyceridemia. Additional factors include family history of diabetes and high blood lipids in people who are not obese. NAFLD refers to a spectrum of conditions ranging from simple fat accumulation in the liver to steatohepatitis, cirrhosis and hepatocellular carcinoma.

- Non-alcoholic fatty liver, or NAFL – A benign condition with simple fat accumulation within liver cells (hepatic steatosis).
- Non-alcoholic steatohepatitis, or NASH – An aggressive form of NAFLD characterized by hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.
- Cirrhosis – 15% to 25% of patients with NASH progress to cirrhosis with consequential complications over 10 to 20 years. Cirrhosis is characterized by the replacement of healthy liver tissue with fibrosis and scar tissue, leading to loss of liver function. NASH cirrhosis is a risk factor for development of hepatocellular carcinoma, or HCC.

NAFLD prevalence is increasing along with the rise of obesity. Advanced NAFLD is now among the most common reasons why patients are referred for liver transplantation.

According to the World Gastroenterology Organization Global Guidelines, the prevalence of NAFLD in children is about 15% in the U.S. and western countries. NAFLD is underdiagnosed in children due to lack of recognition, screening or appreciation of associated complications by healthcare providers. Children may not be recognized as obese during office visits and age-appropriate norms for body mass index may go unacknowledged. Liver disease is screened by measuring serum alanine aminotransferase, or ALT, and aspartate aminotransferase, or AST, starting at 10 years old in obese children and those with a body mass index of 85th to 94th percentile with other risk factors. Currently there are no drug treatment options for NAFLD. Disease management strategies include recommendations for lifestyle changes in diet, exercise and weight reduction.

RP103 as a treatment for NAFLD in children

In 2010, we conducted a Phase 2a clinical trial to examine RP103 as a treatment for NAFLD and NASH in children. Results of this trial with a prototype of RP103 showed that patients exhibited a marked decline in serum transaminase levels during the treatment period of 26 weeks. Seven of 11 juvenile NAFLD patients entering the study with elevated ALT and AST achieved more than 50% reduction in ALT and six of 11 reduced their ALT levels to normal range. AST levels were also improved, with patients averaging 41% reduction by the end of the 26-week treatment phase. This reduction in serum liver enzymes was largely sustained during the 6-month post-treatment monitoring phase. Other important liver function markers showed positive trends, suggesting improvements in hepatic histopathology. These markers included reduced levels of cytokeratin 18, or CK-18, a potential serum marker of disease activity in NASH and NAFLD, which decreased by an average of 45%. Adiponectin levels showed a positive increase by an average of 35% during the treatment period. Reduced adiponectin levels are thought to be a marker of the pathogenesis and progression of NASH and NAFLD.

The ALT and AST reductions achieved in the Phase 2a trial were consistent with ALT and AST reductions seen in patients who achieved a 10% weight loss, although body mass index did not change significantly during both the treatment and post-treatment phases in the Phase 2a clinical trial. In this Phase 2a clinical trial, the prototype of RP103 demonstrated a favorable safety profile, with mean gastrointestinal symptom scores of 1.1 (the maximum score of 14 indicates the most severe gastrointestinal symptoms) at baseline and 0.7 after six months of treatment.

In June 2012, we announced the dosing of the first patient in a Phase 2b clinical trial – Cysteamine Bitartrate Delayed-Release for the Treatment of Non-alcoholic Fatty Liver Disease in Children, or CyNCh, which is evaluating the safety and efficacy of RP103 as a potential treatment of NAFLD in children. The clinical trial is being conducted under a Cooperative Research and Development Agreement, or CRADA, with the National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, part of the National Institutes of Health, or NIH. Upon full enrollment in January 2014, 169 patients were enrolled at 10 U.S. centers in the NIDDK-sponsored NAFLD Clinical Research Network.

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Raptor and NIDDK share the costs of conducting the CyNCh clinical trial. The primary objective of this randomized, multicenter, double-blind, placebo-controlled Phase 2b clinical trial is to evaluate whether 52 weeks of RP103 treatment reverses liver tissue damage caused by NAFLD as measured by changes in NAFLD Activity Score, or NAS, a histological rating scale of disease activity (based on scoring lobular inflammation, hepatocyte ballooning and steatosis from a liver biopsy), in conjunction with no worsening of liver tissue fibrosis. Secondary endpoints include blood markers for liver health including ALT and AST as well as safety and tolerability. Top line clinical trial results for this study are anticipated in the first half of 2015.

RP103 Mechanism in NAFLD

Cysteamine's potent antioxidative properties, including the production of glutathione, may reduce oxidative damage that results from excessive accumulation of fats in liver cells. In addition, cysteamine's anti-fibrotic activity, including inhibiting the production of transglutaminase, may play a role in stabilizing or even reducing the liver fibrosis that occurs in severe cases of NAFLD.

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 U.S. is estimated to be 1 in 40,000 newborns.

RP103 as a treatment for mitochondrial disorders including Leigh Syndrome

We have submitted an investigational new drug application, or IND, to the FDA for the clinical development 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.

The clinical trial is designed to evaluate the safety, tolerability and efficacy of RP103 in patients with genetically confirmed Leigh syndrome as well as patients with other mitochondrial disorders. The clinical plan includes an open label, 24 week, Phase 2/3 study in 32 patients (up to a maximum of 64 patients). Patients with Leigh syndrome are expected to comprise two-thirds of the enrolled population in the study. Initiation of the clinical trial is planned for the first half of 2014 at four clinical sites in the U.S. Based on an adaptive design statistical plan, we will conduct interim analyses after 12 patients and again after 24 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, or NPMDS, 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 2014.

Other Clinical-Stage Product Candidates

Convivia™ for ALDH2 Deficiency

We are developing Convivia, our proprietary oral formulation of 4-methylpyrazole, or 4-MP, for the potential treatment of acetaldehyde toxicity resulting from ALDH2 deficiency.

We own the intellectual property portfolio pertaining to Convivia, including method of use and formulation patents. In June 2010, we granted an exclusive license to commercialize Convivia in Taiwan to Uni Pharma Co., Ltd. Under this agreement, Uni Pharma is responsible for clinical development, registration and commercialization of Convivia in Taiwan. We continue to seek partners in other Asian countries to license Convivia.

Preclinical Product Candidates

Our preclinical programs include our cysteamine dioxygenase, or ADO, program, to improve treatment of diseases for which cysteamine is therapeutic and our HepTide™ program to treat hepatocellular carcinoma and other cancers susceptible to induced lysosomal storage.

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Future Activities

We expect that our near-term efforts will be focused on:

- Increasing sales of PROCYSBI and providing comprehensive reimbursement and adherence support to commercial patients in the U.S.;
- Negotiating pricing and reimbursement in specific European countries and launching PROCYSBI in the first EU country in the first half of 2014;
- Filing a New Drug Submission, or NDS, for PROCYSBI with Health Canada in the second half of 2014;
- Continuing a clinical trial to evaluate PROCYSBI in cystinosis patients that are cysteamine-naïve, as well as other supporting trials in underdeveloped markets;
- Developing select global markets with significant numbers of known cystinosis patients;
- Screening for undiagnosed and unidentified late-onset nephropathic cystinosis;
- Supporting clinical programs and developing regulatory strategies for the use of RP103 as a potential treatment of HD in adults;
- Supporting our clinical trials of RP103 for the potential treatment of NAFLD in children;
- Supporting clinical programs evaluating RP103 for the potential treatment of mitochondrial disorders;
- Supporting our novel preclinical programs and identifying promising in-licensing candidates; and
- Continuing the development of our RP103 clinical pipeline in other indications.

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 5 Hamilton Landing, Suite 160, Novato, CA 94949. Our phone number is (415) 408-6200.

As of February 28, 2014, there were 62,479,286 shares of our common stock outstanding. Our common stock currently trades on the NASDAQ Global Market under the ticker symbol "RPTP."

Corporate History

In September 2009, our subsidiary merged with and into Raptor Pharmaceuticals Corp., a Delaware corporation, or RPC, pursuant to which the stockholders of RPC received shares of our common stock in exchange for their shares of stock and RPC survived as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger, we changed our corporate name from "TorreyPines Therapeutics, Inc." to "Raptor Pharmaceutical Corp." At the time of the 2009 Merger, RPC had two principal subsidiaries, Raptor Discoveries, a development-stage research and development company, and Raptor Therapeutics, which focused on developing clinical-stage drug product candidates through to commercialization and, in connection with the 2009 Merger, these two subsidiaries became our subsidiaries. In December 2012, the two principal subsidiaries were merged and currently operate under the name Raptor Pharmaceuticals Inc. Due to the amount of our stock issued to the stockholders of RPC in the 2009 Merger, RPC was treated as the "accounting acquirer" in the merger, and its board of directors and officers manage and operate the combined company. In December 2011, we merged RPC with and into us and it ceased to exist as a separate company. TorreyPines Therapeutics was incorporated in July 1997 under the name "Axonyx, Inc." and RPC was incorporated in May 2006 under the name "Highland Clan Creations Corp."

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Proprietary Rights

IP Protection for RP103 for Cystinosis and Other Indications

Our composition and method of use patents

We have an exclusive worldwide license from the University of California, San Diego, or UCSD, to issued and pending patents covering composition of matter, or COM, method of use, or MOU, and composition for use, or CFU, for RP103, a Delayed Release form of cysteamine bitartrate, to treat cystinosis and other therapeutic indications. U.S. Patent No. 8,129,433 (expires 2027), for which applications are pending in certain European and other countries, represents a COM patent, which covers the composition comprising cysteamine and any material that provides increased delivery to the small intestine and composition comprising enterically coated cysteamine. U.S. Patent No. 8,026,284 (expires 2027), for which applications are pending in certain European and other countries, represents a MOU patent, which covers method of administering cysteamine composition that increases delivery to small intestine, at a dosing schedule less than four times daily, including two times daily and contains pharmacokinetic claims. European Patent 1919458 (expires 2027), represents a CFU patent and covers the use of any composition of enterically coated cysteamine or cystamine, regardless of the specific formulation, for treating cystinosis two times a day.

Our cysteamine intellectual property to treat metabolic and neurodegenerative conditions

We also have a worldwide exclusive license from UCSD to U.S. Patent Nos. 7,994,226 and 8,263,662 (expire 2028) and MOU patents which cover cysteamine and related compounds for the potential treatment of NASH and NAFLD, respectively. Additionally, we have a worldwide exclusive license from UCSD to international patent application PCT/U.S. 2012/66288, a MOU patent covering the use of cysteamine and related compounds to treat ischemic injury. Our exclusive worldwide license from the Weizmann Institute includes U.S. Patent Nos. 6,794,414 and 6,355,690, MOU patents which cover the use of transglutaminase inhibitors (a class of molecules which includes cysteamine) to treat HD and other neurodegenerative diseases mediated by transglutaminase, or other diseases associated with CAG repeat expansion.

In May 2012, we acquired exclusive rights to U.S. patent application 13/277,942 related to cysteamine and related compounds in the potential treatment of parasitic diseases, including malaria, from McGill University, or McGill, in Montreal, Canada. The McGill application covers the use of cysteamine and related compounds in the potential treatment of malaria in combination with artemisinin, the current standard of care. Researchers at McGill reported that, in mouse models of malaria, the combination reduced parasite levels in red blood cells and improved survival rates compared to artemisinin alone.

In June 2012, we acquired exclusive rights to international patent application PCT/CA 2012/050106, related to cysteamine and related compounds for the potential treatment of Parkinson's disease from Université Laval, or Laval, Quebec, Canada. Our agreement with Laval provides exclusive rights to technology related to the use of cysteamine and related compounds to potentially modify the progression of Parkinson's disease. Researchers at Laval reported that administration of cystamine (an oxidized form of cysteamine) in an animal model of Parkinson's disease showed signs of preventing neuron loss and rescuing neurons undergoing a degenerative process. Signs of restoration of neuronal loss and partial reversal of behavioral impairments were also observed.

In September 2012, we acquired exclusive worldwide rights to international patent application PCT/US11/57935, related to cysteamine and related compounds in the potential treatment of tissue fibrosis from the Seattle Children's Research Institute, or SCRI. Researchers at SCRI demonstrated in preclinical studies in mice that daily treatment with cysteamine attenuated renal fibrosis, with up to 25% reduction of extracellular fibrotic material observed over a 21-day study period.

In May 2013, we acquired exclusive world-wide rights to international patent application PCT/EP2011/068576, an MOU patent covering use of cysteamine and related compounds to treat MECP-2 associated disorders including Rett Syndrome, from the Technology Transfer Accelerator of South Eastern France (SATT Sud Est) that represents the French medical research organizations where the technology was invented, including the Institut Curie, INSERM and Aix-Marseille Université.

Trademarks

The trademark "Raptor" is registered in the U.S. and the EU, and applied for in certain other countries. We also own applications and registrations for various other marks in the U.S. and certain countries throughout the world. All third party trademarks identified in this Annual Report on Form 10-K belong to their respective owners.

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Regulatory Exclusivity

Orphan Drug Designation

We have been granted Orphan Drug Designation from the FDA for use of PROCYSBI to manage cystinosis, and the use of RP103 to potentially treat HD, pancreatic cancer and Batten Disease. The Orphan Drug Act of 1983 generally provides incentives, including marketing exclusivity, user fee waivers and tax benefits, to companies that undertake development and marketing of products to treat relatively rare diseases, which are defined as diseases for which there is a patient population of fewer than 200,000 persons in the U.S. or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the U.S. A drug that receives orphan drug designation may receive up to seven years of exclusive marketing in the U.S. for that indication, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. A drug may be entitled to an additional six months of exclusive marketing if it satisfies the requirements for pediatric exclusivity; we have applied for this additional six-month pediatric extension for PROCYSBI.

PROCYSBI has also been granted Orphan Drug Designation and awarded 10 years of marketing exclusivity by the European Medicines Agency, or EMA, for treatment of cystinosis. We plan to submit an application to EMA for Orphan Drug Designation for RP103 for potential treatment of HD in the first half of 2014.

Competition

Cystinosis

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is marketed as a systemic cystine-depleting therapy for cystinosis in the U.S. by Mylan Pharmaceuticals, and by Orphan Europe in markets outside of the U.S. Cystagon was approved by the FDA in 1994 and by EMA in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the U.S. and Europe are pursuing potential cures for cystinosis through gene therapy and stem cell therapy, as well as pro-drug and pegylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

Huntington's Disease

We are not aware of any available treatments to slow the progression of HD. There is only one approved treatment available for specific symptoms of HD, Xenazine® to treat uncontrollable movements (chorea) that result from the disease. There are several pharmaceutical companies pursuing potential cures and disease modifying treatments for HD, as well as numerous academic and foundation sponsored research efforts. To our knowledge, our product candidate, RP103, is the only compound in clinical development which specifically targets deficient BDNF with the goal of slowing disease progression.

Companies with HD product candidates in development include Auspex, Prana, NeuroSearch, Omeros, Teva, Eli Lilly & Co. and Pfizer. Several other companies have drug candidates in preclinical development. Additionally, nutritional supplements including creatine and coenzyme Q10 have been investigated as potential treatments for HD. The Huntington Study Group sponsors numerous studies of potential therapies for HD, including coenzyme Q10 and the antibiotic minocycline.

NASH and NAFLD

We are not aware of any currently approved treatment options for NASH or NAFLD. Weight loss, healthy diet, abstinence from alcohol and increased physical activity are typically suggested to slow the progression of NASH and NAFLD. There are numerous therapies being studied for NASH, including obeticholic acid, a farnesoid X receptor (FXR) agonist (Intercept Pharmaceuticals), lysyl oxidase-like 2 inhibitor (Gilead), PPAR alpha and delta agonist

(Genfit), Diacylglycerol acyl transferase-1 inhibitor (Novartis) and galectin inhibitor (Galectin), as well as anti-oxidants.

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ALDH2 Deficiency

We are not aware of any pharmaceutical products currently approved for ALDH2 deficiency, either in the U.S. or internationally. There are several non-prescription, nutritional supplements available which purport to mitigate the side effects that result from drinking by people with ALDH2 deficiency. Although we are not aware of any study which has demonstrated the efficacy of such non-pharmaceutical alternatives, these products may compete with our ALDH2 deficiency product candidate if it is approved for marketing.

Government Regulations of the Biotechnology Industry

Regulation by governmental authorities in the U.S. and foreign countries is a significant factor in the development, manufacture and expected marketing of our drug product candidates and in our ongoing research and development activities. The nature and extent to which such regulation will apply to us will vary depending on the nature of any drug product candidates developed. We anticipate that all of our drug product candidates will require regulatory approval by governmental agencies prior to commercialization.

In particular, human therapeutic products are subject to rigorous preclinical and clinical testing and other approval procedures of the FDA and similar regulatory authorities in other countries. Various federal statutes and regulations also govern or influence testing, manufacturing, safety, labeling, storage and record-keeping related to such products and their marketing. The process of obtaining these approvals and the subsequent compliance with the appropriate federal statutes and regulations requires substantial time and financial resources.

Before obtaining regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early clinical trials might not be predictive of results that would be obtained in large-scale testing. Our clinical trials might not successfully demonstrate the safety and efficacy of any product candidates or result in marketable products.

In order to clinically test, manufacture and market products for therapeutic use, we will have to satisfy mandatory procedures and safety and effectiveness standards established by various regulatory bodies. In the U.S., the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, as amended, or FDCA, and the regulations promulgated thereunder, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, record keeping, approval, advertising, and promotion of our current and proposed product candidates. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The steps required by the FDA before new drug products may be marketed in the U.S. include:

- completion of extensive preclinical studies performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- the submission to the FDA of a request for authorization to conduct clinical trials in an investigational new drug application, or IND, which must become effective before clinical trials may commence;
- approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study may be initiated;
- completion of adequate and well-controlled human clinical trials to establish and confirm the safety and efficacy of a drug candidate for the proposed indication;
- completion of process validation, quality product release and stability;
- submission to the FDA of a new drug application, or NDA, for the drug candidate for marketing approval;
- potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with the FDA's current Good Manufacturing Practice, or cGMP, requirements; and
- review and approval of the NDA by the FDA before the product may be sold commercially.

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Preclinical testing includes laboratory evaluation and characterization of the safety and efficacy of a drug and its formulation. Preclinical testing results are submitted to the FDA as a part of an IND which must become effective prior to commencement of clinical trials. Clinical trials are typically conducted in three sequential phases following submission of an IND. Phase 1 represents the initial administration of the drug to a small group of humans, either patients or healthy volunteers, typically to test for safety (adverse effects), dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology, and, if possible, to gain early evidence of effectiveness. Phase 2 involves studies in a small sample of the actual intended patient population to assess the efficacy of the drug for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects. Once an investigational drug is found to have some efficacy and an acceptable safety profile in the targeted patient population, Phase 3 studies are initiated to further establish clinical safety and efficacy of the therapy in a broader sample of the general patient population, in order to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for any physician labeling. During all clinical studies, we must adhere to GCP or good clinical practices, standards. The results of the research and product development, manufacturing, preclinical studies, clinical studies and related information are submitted in an NDA to the FDA.

The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate. The process of completing clinical testing and obtaining FDA approval for a new drug is likely to take a number of years and require the expenditure of substantial resources. If an application is submitted, there can be no assurance that the FDA will review and approve the NDA.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is subject to a substantial application user fee. Applications for orphan drug products are exempted from the NDA user fees, unless the application includes an indication for other than a rare disease or condition.

An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Once an NDA has been submitted, the FDA's goal is to review the application within 10 months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by FDA requests for additional information or clarification. In addition, an application may be referred to an advisory committee, which is a panel of independent experts, to review, evaluate and provide a recommendation to the FDA as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it typically follows such recommendations and considers them carefully when making approval decisions.

Before obtaining FDA approval for each product, the FDA typically will inspect the facility or facilities where the product is manufactured and will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP requirements. Following approval, each product manufacturing establishment must be registered with the FDA and its quality control and manufacturing procedures must continue to conform and adhere at all times to the FDA's cGMP regulations. The FDA and other government agencies regularly inspect manufacturing facilities for compliance with these requirements. If, as a result of these inspections, the FDA determines that any equipment, facilities, laboratories or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of the manufacturing operations. Manufacturers must expend substantial time, money and effort in the area of production and quality control to ensure full technical compliance with these standards.

Even after initial FDA approval has been obtained, further studies, including a commitment to conduct post-market studies, would be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested and approved. Also, the FDA will require post-market reporting. Results of post-marketing programs, including Phase 4 clinical studies or post-market surveillance, might limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process, labeling or a change in manufacturing facility, submission and approval of an NDA supplement might be required.

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Failure to comply with applicable FDA requirements may result in a number of consequences that could materially and adversely affect us. Failure to adhere to approved trial standards and GCPs in conducting clinical trials could cause the FDA to place a clinical hold on one or more studies which would delay research and data collection necessary for product approval. Noncompliance with GCPs could also have a negative impact on the FDA's evaluation of an NDA. Failure to adhere to GCPs, cGMPs and other applicable requirements could result in FDA enforcement action and in civil and criminal sanctions, including but not limited to fines, seizure of product, refusal of the FDA to approve product approval applications, withdrawal of approved applications, and prosecution. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a Risk Evaluation and Mitigation Strategies, or REMS, program. The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval might be longer or shorter than that required for FDA approval. Although there are some procedures for unified filings for some European countries, in general, each country at this time has its own procedures and requirements. There can be no assurance that any foreign approvals would be obtained.

In addition to the regulatory framework for product approvals, we and our collaborative partners must comply with federal, state and local laws and regulations regarding occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control, and other local, state, federal and foreign regulations. All facilities and manufacturing processes used by third parties to produce our drug candidates for clinical use in the U.S. must conform with cGMPs. These facilities and practices are subject to periodic regulatory inspections to ensure compliance with cGMP requirements. Their failure to comply with applicable regulations could extend, delay, or cause the termination of clinical trials conducted for our drug candidates or of manufacturing and sale of any of our products approved for sale. We cannot accurately predict the extent of government regulation that might result from future legislation or administrative action.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. Based on results of clinical studies submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of 10 months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or

lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a Breakthrough Therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and 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.

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European Union Drug Review and Approval

In the EEA (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MA:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the CHMP of the EMA, is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes and auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in other Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Orphan Designation and Exclusivity

The Orphan Drug Act provides incentives for the development of products intended to treat rare diseases or conditions. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that the cost of developing and making a drug product available in the U.S. for this type of disease or condition will be recovered from sales of the product. If a sponsor demonstrates that a drug is intended to treat rare diseases or conditions, the FDA will grant orphan designation for that product for the orphan disease indication. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

Orphan drug designation provides manufacturers with research grants, tax credits and eligibility for orphan drug exclusivity. If a product that has orphan drug designation subsequently receives the first FDA approval of the active moiety for that disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which for seven years prohibits the FDA from approving another product with the same active ingredient for the same indication, except in limited circumstances. If a drug designated as an orphan product receives marketing approval for an indication broader than the orphan indication for which it received the designation, it will not be entitled to orphan drug exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of for the same product but for a different indication for which the orphan product has exclusivity. As a result, even if we obtain orphan exclusivity, we may still be subject to competition.

In the EU, the EMA's Committee for Orphan Medicinal Products, or COMP, 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 European Union Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would

be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. In the EU, orphan drug designation entitles a party to financial incentives such as reduction of 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. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

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Pediatric Studies and Exclusivity

NDAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA or Biologic License Application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical study is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application relying on the NDA sponsor's data.

Hatch-Waxman Amendments and Exclusivity

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the approved branded reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the branded reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the Orange Book. Any applicant who files an abbreviated new drug application, or ANDA, seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. This last certification is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA or 505(b)(2) application refers. The applicant may also elect to submit a "section viii" statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent.

If the reference NDA holder and patent owners assert a patent challenge directed to one of the Orange Book listed patents within 45 days of the receipt of the paragraph IV certification notice, the FDA is prohibited from approving the application until the earlier of 30 months from the receipt of the paragraph IV certification expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired. Specifically, the holder of the NDA for the listed drug may be entitled to a period of non-patent exclusivity, during which the FDA cannot approve an ANDA or 505(b)(2) application that relies

on the listed drug. For example, a pharmaceutical manufacturer may obtain five years of non-patent exclusivity upon NDA approval of a new chemical entity, or NCE, which is a drug that contains an active moiety that has not been approved by FDA in any other NDA. An "active moiety" is defined as the molecule or ion responsible for the drug substance's physiological or pharmacologic action. During the five-year exclusivity period, the FDA cannot accept for filing any ANDA seeking approval of a generic version of that drug or any 505(b)(2) NDA for the same active moiety and that relies on the FDA's findings regarding that drug, except that FDA may accept an application for filing after four years if the follow-on applicant makes a paragraph IV certification.

A drug, including one approved under Section 505(b)(2), may obtain a three-year period of exclusivity for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. Should this occur, the FDA would be precluded from approving any ANDA or 505(b)(2) application for the protected modification until after that three-year exclusivity period has run. However, unlike NCE exclusivity, the FDA can accept an application and begin the review process during the exclusivity period.

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Coverage and Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage and reducing reimbursements for medical products and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for PROCYSBI and our drug candidates or a decision by a third-party payor to not cover PROCYSBI and our drug candidates could reduce physician utilization of our products and have a material adverse effect on our sales, results of operations and financial condition.

Other Healthcare Laws

We are also subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. Further, the recently enacted Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Health Care Reform Law, among other things, amends the intent requirement of the federal Anti-Kickback Statute and the criminal statute governing healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them. In addition, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute. The majority of states also have anti-kickback laws which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Health Care Reform Law, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not

timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and submit reports to the government by March 31, 2014 and the 90th day of each subsequent calendar year. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

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Legal Proceedings

We know of no material, active or pending legal proceedings against us, nor are we involved as a plaintiff in any material proceedings or pending litigation. There are no proceedings in which any of our directors, officers or affiliates, or any registered or beneficial stockholders are an adverse party or have a material interest adverse to us.

Research and Development

We have an active research and development effort. Our plan is to focus our research and development efforts in the discovery, research, preclinical and clinical development of our clinical drug candidates in order to provide therapies that we believe will be safer, less intrusive and more effective than current approaches in treating a wide variety of disorders. During the year ended December 31, 2013, the four-month transition period ended December 31, 2012 and the fiscal years ended August 31, 2012 and 2011, we incurred approximately $29.2 million, $8.9 million, $21.4 million and $14.8 million, respectively, in research and development expenses.

Operating Segment and Geographic Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by a company in deciding how to allocate its resources and to assess its performance. We have reviewed how we allocate our resources and analyze performance worldwide and have determined that, because employees work on integrated programs in the U.S. and in Europe, encompassing all stages of product development and commercialization, we operate in one segment.

Compliance with Environmental Laws

We estimate the annual cost of compliance with environmental laws, comprised primarily of hazardous waste removal, will be nominal.

Employees

As of December 31, 2013, we had 70 full time employees (65 and 5 in the U.S. and EU, respectively) and 2 U.S. part-time employees. Of the 70 employees, 40 are sales and marketing and general and administrative personnel and 30 are in manufacturing, quality control and assurance and research and development. Based on our current plan, over the next 12-month period we intend to expand our U.S. and EU employee base across all functions in the Company.

Facilities

Our primary offices are located at 5 Hamilton Landing, Suite 160, Novato, CA 94949. Our main phone number is (415) 408-6200 and our facsimile number is (415) 382-8002.

Website

Our corporate website is located at www.raptorpharma.com. Any information contained in, or that can be accessed through, our website is not incorporated by reference into, nor is it in any way a part of, this Annual Report on Form 10-K.

Available Information

We are subject to the reporting requirements under the Exchange Act. Consequently, we are required to file reports and information with the SEC, including reports on the following forms: annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. These reports and other information concerning us may be accessed through the SEC's website at www.sec.gov and on our website at www.raptorpharma.com. Such filings are placed on our website as soon as reasonably practicable after they are filed with the SEC.

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ITEM 1A: RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below, together with the other information contained in this Annual Report on Form 10-K. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Associated with Commercialization and Product Development

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

PROCYSBI is our only product currently approved for marketing and, as a result, our operating results are substantially dependent on the commercial success of PROCYSBI, for which we commenced marketing in the U.S. in June 2013. In the U.S., we are permitted to market PROCYSBI only for the management of nephropathic cystinosis in adults and children six years and older. In September 2013, we received marketing authorization from the European Commission, which 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 Free Trade Association, or EFTA) for the treatment of proven nephropathic cystinosis; however, we have not yet commercially launched PROCYSBI in the EU. We believe that the trading price of our common stock will be substantially affected by our results of operations and, in particular, net product sales of PROCYSBI. We do not have prior experience in commercializing therapeutics. If PROCYSBI sales do not meet expectations, our stock price may not increase or could significantly decrease. The successful commercialization of PROCYSBI will depend on several factors, including:

- growing sales of PROCYSBI in the U.S.;
- the negotiation and agreement on an acceptable prices in EU countries and other select territories, and reimbursement at the country-specific price;
- the successful commercial launch of PROCYSBI in the EU and other select territories;
- acceptance of PROCYSBI by physicians, parents, patients and cystinosis research/advocacy organizations including the conversion from the existing standard of care to PROCYSBI;
- coverage and reimbursement for PROCYSBI from commercial health plans and government health programs, which we refer to collectively as third-party payors;
- compliance with regulatory requirements including fulfilling any FDA and EC required post-approval commitments;
- provision of affordable out-of-pocket cost to patients and/or other programs to ensure patient access to PROCYSBI in the U.S.;
- approval by other country regulatory agencies of appropriate product labeling for PROCYSBI;
- agreements with wholesalers, distributors and pharmacies on commercially reasonable terms;
- manufacture and supply of adequate quantities of PROCYSBI to meet commercial demand; and
- development and maintenance of intellectual property protection for PROCYSBI.

If we fail to grow sales of PROCYSBI in the U.S. or successfully commercialize PROCYSBI in the EU within a reasonable time period, we may never become profitable and may be unable to sustain our business, and our business, financial condition and results of operations will be adversely affected.

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

PROCYSBI may not attain or maintain market acceptance among physicians, patients, patient families, third-party payors or the healthcare community compared to the current standard of care. We believe that the degree of market acceptance and our ability to generate significant product sales of PROCYSBI will depend on a number of factors, including:

- availability and relative efficacy, safety and ease of administration of alternative treatments;
- the price of our product, both in absolute terms and relative to alternative treatments;
- timing of market introduction of our product as well as competitive drugs;
- efficacy, safety and prevalence and severity of any side effects of PROCYSBI;
- identification of currently diagnosed and undiagnosed patients and continued growth of the cystinosis market;
- acceptance by patients, patient families and primary care and other specialists including conversion from the existing standard of care;
- continued patient adherence to therapy;
- the effect of current and future healthcare laws;
- availability of coverage and adequate reimbursement and pricing from third-party payors; and
- breadth of product labeling or product insert requirements of the FDA, EC or other regulatory authorities.

If PROCYSBI does not achieve and maintain significant market acceptance among physicians, patients, patient families, third-party payors or the healthcare community, our ability to generate revenues from PROCYSBI will be materially and adversely affected.

The amount of our product sales of PROCYSBI in the EU is dependent upon the pricing and reimbursement guidelines adopted in each of the various countries in the EU, which levels may be below our current expectations.

We have not yet priced PROCYSBI in any countries in the EU. While we are developing estimates of anticipated pricing, one or more EU countries may not support our anticipated pricing and reimbursement for PROCYSBI, particularly in light of the budget crises faced by a number of countries in the EU, which would negatively affect anticipated revenue from PROCYSBI. The pricing and reimbursement process in the EU can be lengthy and involved, and we do not have significant experience with this process. Failure to timely complete the pricing and reimbursement process in the EU will delay our ability to market PROCYSBI in the EU and derive product sales in that region.

If we are unable to expand the use of RP103 and receive regulatory approval for any other indication, we may delay or cease some of our product development activities, which would adversely affect the long term value of RP103 and our growth prospects.

We must obtain and maintain appropriate pre-market 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. In the U.S., we are permitted to market RP103 only for the management of nephropathic cystinosis in adults and children six years and older under the brand name PROCYSBI. We are permitted to market PROCYSBI in the EU as an orphan medicinal product for the treatment of proven nephropathic cystinosis. We do not have approval of RP103 in any other market nor for any other disease indication. A new drug application, or NDA, submitted to the FDA or marketing authorization application, or MAA, submitted to the EMA must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls, to 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.

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Obtaining approval of an NDA, MAA or any other filing for marketing authorization in a foreign country 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, including the substantial discretion of the regulatory authorities. The FDA, EC or other regulatory authorities may delay, limit or deny approval of RP103 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;
- may not find the data from preclinical studies and clinical trials sufficient to demonstrate that a product candidate has adequate clinical and other benefits or an adequate safety profile; or may disagree with our interpretation of data from preclinical studies or clinical trials and require that we conduct additional trials;
- regulatory authorities may not accept data generated at our clinical trial sites;
- regulatory authorities may have difficulties scheduling an advisory committee meeting (or equivalent, if required) in a timely manner or the advisory committee 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, limitations on approved labeling or distribution and use restrictions;
- 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 impose limitations on approved labeling, thus introducing reimbursement complications which may limit access for intended uses or limit the commercial profile of the drug;
- 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 process, specifications or third-party suppliers or contract manufacturers;
- we may not be able to validate our manufacturing process to the satisfaction of the regulatory authorities, or they may not agree with our plan for potential retrospective validation; or
- regulatory authorities may change approval policies or adopt new regulations.

If we fail to gain regulatory approval for RP103 for other indications, we will have to delay or terminate some or all of our research product development programs and our business, financial condition and results of operations will be adversely affected.

We do not have internal manufacturing capabilities. During 2014 and throughout most of 2015, we expect to continue to rely on a single supplier for the active pharmaceutical ingredient and a single third-party manufacturer for the conversion to finished drug product. If we are unable to obtain an adequate supply of our drugs, our reputation will be harmed, our revenues will be delayed or diminished and our financial results will be adversely affected.

Using external CMOs under contract, we currently manufacture commercial and clinical quantities of PROCYSBI and RP103 for the indications under development. We rely on single manufacturing sources for our cysteamine active pharmaceutical ingredient, or API, and finished products. Our ability to obtain sufficient quantities of PROCYSBI and RP103 is constrained by limited supplies of raw materials and capacity and output of these manufacturers, which may have a material adverse impact on sales of PROCYSBI and the availability of product for our clinical trials. While we have entered into an agreement with a second tablet manufacturer, we expect that this second manufacturer will not be able to produce finished products for commercial sale until the latter part of 2015. Furthermore, any reduction or interruption in our supply of API from the single source supplier and of finished goods from our contract manufacturer, and efforts to identify and qualify alternative sources of API supply, could result in significant additional operating costs, interruptions in product supply and delays in sales of PROCYSBI and in developing RP103 for HD, NAFLD and Leigh's syndrome. In addition, supply arrangements from alternative sources may not be available on acceptable economic terms, if at all.

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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 to commercial requirements. Difficulties may arise related to production costs and yields, quality control, including stability of the product or product candidates 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. In addition, due to our small patient population, the manufacture of our drug may be given lower prioritization on the production line if manufacturing is decided by scale.

We depend on our third-party supplier and manufacturers for compliance with the FDA's cGMP requirements and other FDA requirements, Drug Enforcement Administration's regulations and other rules and regulations prescribed by applicable non-U.S. regulatory authorities. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with good manufacturing practices, or cGMP, requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to market PROCYSBI and to develop, obtain regulatory approval for or market our product candidates, if approved. If we or our third-party suppliers and manufacturers fail to comply with applicable regulatory requirements, a regulatory agency may issue warning letters or untitled letters; seek an injunction or impose civil or criminal penalties or monetary fines; suspend or withdraw regulatory approval; 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.

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, financial condition and results of operations would be adversely affected.

PROCYSBI is, and any other future product candidates, if approved, will be, subject to extensive and ongoing regulatory requirements and continued regulatory review, which will result in significant expense. Additionally, PROCYSBI and our future product candidates, if approved, may be subject to labeling and other restrictions or potential market withdrawal, and we may be subject to penalties and litigation if we fail to comply with regulatory requirements or experience problems with our products.

Our manufacturing processes, labeling, packaging, distribution, storage, adverse event reporting, dispensation, distribution, advertising, promotion and recordkeeping are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of product registration, as well as continued compliance with cGMPs, GCPs, good distribution practices, or GDPs, and good laboratory practices, or GLPs. If we do not comply with applicable regulations and requirements, the range of possible sanctions includes adverse publicity, product recalls or seizures, fines, total or partial suspensions of production and/or distribution, suspension of marketing applications, withdrawal of a product's approval and enforcement actions, including injunctions and civil or criminal prosecution. In addition, if we or a regulatory agency discover previously unknown problems with PROCYSBI, such as adverse events of unanticipated severity or frequency, or identify data that suggest that PROCYSBI may present a risk to safety, the regulatory authorities could withdraw our product approval, suspend production or place other marketing restrictions on our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, our growth prospects and our operating results will be adversely affected.

Moreover, any regulatory approvals that we obtain will be subject to limitations on the approved indicated uses for which the product may be marketed or the conditions of approval, or contain requirements for potentially costly

post-market testing and surveillance to monitor the safety and efficacy of the product. The FDA and EC strictly regulate the promotional claims that may be made about prescription products and our product labeling, advertising and promotion is subject to continuing regulatory review. Physicians nevertheless may prescribe our product to their patients in a manner that is inconsistent with the approved label, or that is off-label. The FDA, the Competent Authorities of the Member States of the Economic European Area, or EEA, and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and if we are found to have improperly promoted off-label uses we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

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In addition, engaging in improper promotion of our products for off-label uses in the U.S. can subject us to false claims litigation under federal and state statutes, which can lead to consent decrees, civil money penalties, restitution, criminal fines and imprisonment, and exclusion from participating in Medicare, Medicaid and other federal and state health care programs. These false claims statutes in the U.S. 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 Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay 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.

In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated, and the direct-to-consumer promotion of prescription pharmaceuticals is not permitted. The Member States of the EEA have also adopted laws against misleading and unfair advertising. In addition, some Member States require the notification and/or prior authorization of promotional or advertising materials directed at health care professionals. Failure to comply with these regulations can lead to the imposition of administrative fines and criminal penalties, civil litigation leading to injunctive relief to stop the advertising, corrective statements, or damages.

If serious adverse side effects become associated with PROCYSBI, our business will be harmed.

The prescribing information for PROCYSBI includes several warnings relating to observed adverse reactions of cysteamine bitartrate usage. These adverse reactions were not observed in our clinical trials supporting PROCYSBI's NDA and MAA, but were required on our label due to our submission of a 505(b)(2) application in the U.S. and a hybrid application in the EU. The FDA may require products approved under Section 505(b)(2) of the FDCA to bear the same or similar warning statements as the reference product. We expect to update adverse reactions listed in the prescribing information 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 EMA or other regulatory agencies could modify or revoke our marketing approval, require us to modify our label, or require us to suspend production, or we may choose to withdraw PROCYSBI from the market. If this were to occur, we may be unable to 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 PROCYSBI. Any such side effects or related claims could have a material adverse effect on our business, financial condition and results of operations.

See also the risk factor titled "We may be subject to product liability claims."

Pressure on drug product third-party payor coverage, reimbursement and pricing may impair our ability to be reimbursed for PROCYSBI and our other future product candidates at prices or on terms sufficient to provide a viable financial outcome.

Market acceptance and sales of PROCYSBI and any product candidates that we may develop will depend in large part on third-party payor coverage and reimbursement policies and may be affected by future healthcare reform measures in the U.S. as well as the EU and other key international markets. The continuing efforts of governmental and 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 medical products and services, particularly for new and innovative products and therapies, may result in downward pressure on product pricing, reimbursement and utilization, which may adversely affect our product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, drug coverage and reimbursement policies and pricing in general. Moreover, private health insurers and other third-party payors in the U.S. often follow the coverage and reimbursement policies of government payors, including the Medicare or Medicaid programs. In the U.S., third-party payors are shifting their cost containment measures to specialty products and high-cost drugs and PROCYSBI may be a target of such measures.

Beginning April 1, 2013, Medicare payments for all items and services under Part A and B, including drugs and biologicals, and most payments to plans under Medicare Part D were reduced by 2% under the automatic spending reductions, or sequestration, required by the Budget Control Act of 2011, or BCA, as amended by the American Taxpayer Relief Act, or ATRA. The BCA required sequestration for most federal programs, excluding Medicaid, Social Security and certain other programs, because Congress failed to enact legislation by January 15, 2012 to reduce federal deficits by $1.2 trillion over 10 years. As long as BCA cuts remain in effect, they could adversely impact payment for PROCYSBI. In addition, other recent legislative changes that increase manufacturer liability for rebates and other payments under the 340B drug pricing program, the Medicaid Drug Rebate Program and the Medicare Part D prescription drug benefit also could impact our revenues. See the risk factor titled "Enacted and future legislation may increase the difficulty and cost for us to commercialize PROCYSBI or any other product candidate that we develop and affect the prices we may obtain."

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Further, payors also are increasingly considering new metrics as the basis for reimbursement rates, such as average sales price, or ASP, average manufacturer price, or AMP, or actual acquisition cost, or AAC. Although the intent of the changes to reimbursement methodologies generally is 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 PROCYSBI and any product candidates that we may develop. Although to date PROCYSBI has been reimbursed, we do not know whether third-party payors will continue to reimburse PROCYSBI in the U.S. and whether third-party payors will reimburse RP103 and our future products for future commercial indications until we enter into payor negotiations. If coverage and reimbursement are not available or available only to limited levels, we may not be able to generate sufficient revenue to meet our operating costs or to achieve our revenue, cash flow breakeven or profitability goals in the timeframe that we expect, or at all.

Enacted and future legislation may increase the difficulty and cost for us to commercialize PROCYSBI or any other product candidate that we develop and affect the prices we may obtain.

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

The Medicare Prescription Drug Improvement and Modernization Act of 2003, or MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for outpatient drug purchases by those covered by Medicare under a new Part D and introduced a new reimbursement methodology based on average sales prices for Medicare Part B physician-administered drugs. In addition, this legislation authorized Medicare Part D prescription drug plans to use formularies whereby they can limit the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of drug products, there is additional pressure to contain and reduce costs. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors. These cost reduction initiatives and other provisions of the MMA could decrease the coverage and reimbursement that we receive for any approved products, and could seriously harm our business. Manufacturers' contributions to this area, including donut hole coverage (as described below) or potential excise taxes, are increasing and are subject to additional changes in the future.

In 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (together, the "Health Care Reform Law"), a sweeping law intended 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 Health Care Reform Law, among other things, revised the definition of AMP for reporting purposes, which could increase the amount of Medicaid drug rebates to states and extended the rebate program to beneficiaries enrolled in Medicaid managed care organizations. The Health Care Reform Law also 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 U.S. The Health Care Reform Law also expanded the 340B drug discount program (excluding orphan drugs), including the creation of new penalties for non-compliance and included a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, or "donut hole." The Health Care Reform Law includes a provision to increase the Medicaid rebate for line extensions or reformulated drugs, which depending on how this provision is implemented could substantially increase our Medicaid rebate rate (in effect limiting reimbursement for these patients). These and other new provisions are likely to continue the pressure on pharmaceutical pricing, may require us to modify our business practices with healthcare practitioners, and may also increase our regulatory burdens and operating costs. See the risk factor titled "Failure to comply with healthcare regulations may subject us to substantial penalties."

Legislative and regulatory proposals also have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. In addition, 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. Delays in feedback from the FDA may affect our ability to quickly update or adjust our label 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 specifically the commercialization of PROCYSBI.

Failure to comply with healthcare regulations may subject us to substantial penalties.

Although we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, federal and state healthcare laws and regulations pertaining to fraud and abuse, physician payment transparency and privacy and security laws and regulations apply to us and our arrangements with healthcare providers, customers and other entities, including our marketing practices, educational programs and pricing policies. The laws that may affect our ability to operate as a commercial organization include:

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- the federal Anti-Kickback Statute, which prohibits, among other things, persons 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;
- federal false claims laws 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;
- federal criminal laws that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
- the 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 the Centers for Medicare & Medicaid Services, or 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 applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by physicians (as defined above) and their immediate family members and payments or other "transfers of value" to such physician owners and their immediate family members. Manufacturers were required to begin data collection on August 1, 2013 and to report aggregate data to the government by March 31, 2014 with more detailed reports due by August 1, 2014;
- in the EU, in various Member States, including France, the UK, the Netherlands, Italy, or Spain, the legislator or self-regulatory industry bodies have adopted rules requiring the notification and/or publication of certain transfers of value from pharmaceutical companies to health care 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 health care professionals; 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.

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, the Health Care Reform Law further strengthened these laws by amending the intent requirement of the federal anti-kickback and criminal health care fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. In addition, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Moreover, there has been a recent trend of increased federal and state regulation of payments made to physicians for marketing. Certain states mandate implementation of compliance programs and/or the tracking and reporting of gifts, compensation, and other remuneration to physicians. The shifting compliance environment and the need to build and maintain robust and expandable systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increase the possibility that a healthcare company may violate one or more of the requirements.

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 health care providers, some of whom recommend, purchase and/or prescribe our products, could be subject to challenge under one or more of such laws. While these activities are structured to comply with all applicable laws, if

our operations are found to be in violation of 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, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to market PROCYSBI, RP103 and other future drug candidates and adversely impact our financial results. 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 U.S., we could be subject to additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial condition, results of operations and future business prospects."

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

We participate in the Medicaid Drug Rebate Program and other Federal and state government pricing programs in the U.S., and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or 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. 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, and could have a material adverse effect on our results of operations.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by governmental or regulatory agencies and the courts.

In addition, the Office of Inspector General has recently increased its focus on the methodologies used by manufacturers to calculate AMP and best price, or 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 overcharging 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.

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

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

PROCYSBI and our clinical development of RP103 target diseases with small patient populations, including cystinosis and HD, respectively. A key component of the successful commercialization of a drug product for these indications includes identification of patients and a targeted prescriber base for the drug product. Due to small patient populations, we believe that we would need to have significant market penetration to achieve meaningful revenues and identifying patients and targeting the prescriber base are key to achieving significant market penetration. In addition, the per-patient prices at which we sell PROCYSBI (currently an average of $250,000 per year prior to rebates, discounts, distribution fees and not adjusted for patient compliance in the U.S.) and RP103 for these indications will need to be relatively high in order for us to generate an appropriate return for the investment in these product development programs and achieve meaningful gross margins. There can be no assurance that we will be successful in achieving a sufficient degree of market penetration and/or obtaining or maintaining high per-patient prices for PROCYSBI and RP103 for diseases with small patient populations. Further, even if we obtain significant market share for PROCYSBI and RP103, if approved, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share. Furthermore, because the potential target populations are very small, even if we do obtain significant market share for PROCYSBI and RP103, if approved, we may never achieve profitability. Additionally, patients who discontinue therapy or do not fill prescriptions are not easily replaced by new patients, given the limited patient population.

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

As part of our business strategy, we intend to develop RP103 for additional indications and other drugs 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 U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the U.S. In the U.S., 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, with an additional six months if for a pediatric indication. Orphan drug exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective, a subsequent product is deemed clinically superior, or if the manufacturer is unable to deliver sufficient quantity of the drug.

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In the EU, the EMA's Committee for Orphan Medicinal Products, or COMP, 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 Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. An EU orphan drug designation entitles a party to financial incentives such as reduction of 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. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. 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 products that are eligible for orphan drug designation. For eligible drugs, we plan to rely on the orphan exclusivity period to maintain a competitive position. However, if we do not obtain orphan drug exclusivity for RP103 for the potential treatment of HD or other potential indications, or our future relevant drug products do not have strong patent protection, our competitors may then sell the same drug to treat the same condition and our revenues will be reduced. Also, without strong patent protection, competitors may sell a generic version upon the expiration of orphan exclusivity, if our patent position is not upheld.

Even though we have been granted orphan drug designation in the U.S. prior to the approval of RP103 for the potential treatment of 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. The FDA can discontinue Orphan Drug exclusivity after it has been granted if the orphan drug cannot be manufactured in sufficient quantities to meet demand. Positive clinical trial results in any of our RP103 programs increase the risk that Cystagon may be used off-label in those indications in certain geographic areas due to Cystagon's lower cost and our 505(b)(2) filing status.

A breakthrough designation or fast track designation for our drug product candidates, if obtained, may not actually lead to a faster review process.

Under the Prescription Drug User Fee Act, the FDA has a goal of responding to NDAs within 10 months of submission the filing date for standard review, but this timeframe is also often extended. In the future, we may seek approval of our drug candidates under programs designed to accelerate the FDA's review and approval of NDAs. 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 approves a schedule for the remaining information. In some cases, a product may be approved on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Approvals of this kind typically include requirements for appropriate post-approval Phase 4 clinical trials to validate the surrogate endpoint or otherwise confirm the effect of the clinical endpoint. In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, 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, and 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 we cannot assure 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 FDA approval of 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 requesting additional clinical studies (although potentially a post-marketing requirement), during its review. Any request for additional information or clinical data could delay the FDA's timely review of our NDA.

We may not be successful in integrating our European operations with our U.S. operations.

In connection with the anticipated European commercial launch of PROCYSBI, we have expanded our operations in Europe where we expect to continue to add personnel. 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 include the following:

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- the potential strain on our financial and managerial controls and reporting systems and procedures;
- potential miscommunication between U.S. personnel and European personnel due to cultural and language differences;
- the small size of our company and our intention to grow at a consistent but measured pace;
- ability to operate within diverse individual country regulatory and statutory laws; and
- the costs of maintaining EU presence, in-country legal entities and related tax structures.

If we fail to obtain and maintain approval from regulatory authorities in international markets for PROCYSBI, RP103 and any future product candidates for which we have rights in international markets, our market opportunities will be limited and our business will be adversely impacted.

Sales of our products outside of