CONCERT PHARMACEUTICALS, INC.
Form 10-K
March 01, 2016

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

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FORM 10-K

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(Mark One)

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

For the fiscal year ended: December 31, 2015

or

¨ 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: 001-36310

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CONCERT PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

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| | |
|---|---|
| Delaware | 20-4839882 |
| (State or other jurisdiction of incorporation or organization) | (I.R.S. Employer Identification No.) |

99 Hayden Avenue, Suite 500
Lexington, Massachusetts 02421
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (781) 860-0045

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

| Title of each class | Name of each exchange on which registered |
|---|---|
| Common Stock, par value $0.001 per share | The NASDAQ Global Market |

Securities registered pursuant to 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 ¨ No ý

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 ý

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 ý No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, 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 ý No ¨

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Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) 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. ¨

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 definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

| | | | |
|---|---|---|---|
| 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 Exchange Act). Yes ¨ No ý

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2015 was approximately $195,641,000, based on the closing price of the registrant's common stock on the NASDAQ Global Market on that date.

The number of shares outstanding of the registrant's Common Stock as of February 23, 2016: 22,204,347

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PART IV

References to Concert

Throughout this Annual Report on Form 10-K, the "Company," "Concert," "we," "us," and "our," except where the context requires otherwise, refer to Concert Pharmaceuticals, Inc. and its consolidated subsidiary, and "our board of directors" refers to the board of directors of Concert Pharmaceuticals, Inc.

Forward-Looking Information

This Annual Report on Form 10-K contains forward-looking statements regarding, among other things, our future discovery and development efforts, our future operating results and financial position, our business strategy, and other objectives for our operations. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "pro "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug discovery and clinical development activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, our ability to obtain any necessary financing to conduct our planned activities and other risk factors. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the section entitled "Risk Factors" in Part I that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make. Unless required by law, we do not undertake any obligation to publicly update any forward-looking statements.

Part I

Item 1. Business

OVERVIEW

We are a clinical stage biopharmaceutical company applying our extensive knowledge of deuterium chemistry to discover and develop novel small molecule drugs. Incorporation of deuterium into known molecules has the potential to provide better pharmacokinetic or metabolic properties, thereby enhancing their clinical safety, tolerability or efficacy. Our approach starts with approved drugs, advanced clinical candidates or previously studied compounds that may be improved with deuterium substitution. Our technology provides the opportunity to develop products that may compete with the non-deuterated drug in existing markets or to leverage the known activity of approved drugs to expand into new indications. Our DCE Platform® has broad potential across numerous therapeutic areas. The following table summarizes our diverse clinical pipeline of product candidates. All of these candidates are small molecules designed for oral administration.

| Product Candidate | Lead Indication | Status | Worldwide rights |
|---|---|---|---|
| AVP-786<br>Deuterated dextromethorphan | Alzheimer's Agitation<br>Major Depressive Disorder<br>Residual Schizophrenia | Phase 3<br>Phase 2<br>Phase 2 | Avanir Pharmaceuticals |
| CTP-656<br>Deuterated ivacaftor | Cystic Fibrosis | Phase 1 | Concert |
| CTP-730<br>Deuterated apremilast | Inflammation | Phase 1 | Celgene |
| JZP-386<br>Deuterated sodium-oxybate | Narcolepsy | Phase 1 | Jazz Pharmaceuticals |

OUR STRATEGY

Our strategy is to apply our deuterium technology to well characterized molecules in order to leverage their known safety and efficacy profile. We select pipeline candidates based on the medical needs of patients, commercial opportunity, regulatory considerations, and competitive landscape.

Our approach aims to enable drug discovery and clinical development that is more efficient and less expensive than conventional small molecule drug research and development. Key elements of our strategy include:

- Using deuterium technology to develop deuterated product candidates with substantially improved safety, tolerability or efficacy profiles to compete directly with the non-deuterated compound in its approved indication. In addition, we expect to develop deuterated product candidates that are based on approved drugs but for new indications that we believe are promising in view of the known biology of the approved drug.

- Developing our deuterated product candidates quickly through proof-of-concept clinical trials, which could be as early as Phase 1, and then determining whether to advance it independently or with a partner; and

- Commercializing product candidates where they can be marketed by a small, focused sales force or seeking partners based on strategic considerations.

DEUTERIUM

Due to its natural abundance, the average adult human body contains approximately two grams of deuterium. While essentially identical to hydrogen in size and shape, deuterium differs from hydrogen in that it contains an additional neutron. As a result, deuterium forms a more stable chemical bond with carbon than does hydrogen. The deuterium-carbon bond is typically six to nine times more stable than the hydrogen-carbon bond. This has important

implications for drug development because drug metabolism often involves the breaking of hydrogen-carbon bonds.

Because deuterium forms more stable bonds with carbon, deuterium substitution can in some cases alter drug metabolism, including through improved metabolic stability, reduced formation of toxic metabolites, increased formation of desired active metabolites, or a combination of these effects. At the same time, because deuterium closely resembles hydrogen, the substitution of deuterium for hydrogen has generally been found not to materially alter the intrinsic biological activity of a compound. Deuterated compounds can generally be expected to retain biochemical potency and selectivity similar to their hydrogen analogs. The effects, if any, of deuterium substitution on metabolic properties are highly dependent on the specific molecular positions at which deuterium is substituted for hydrogen. In addition, the metabolic effects of deuterium substitution, if any, are unpredictable, even in compounds that have similar chemical structures.

Potential advantages of product candidates based on our DCE Platform

Using our DCE Platform we create novel drugs designed to have superior properties - including enhanced clinical safety, tolerability or efficacy - based on compounds that have established pharmacological activity. In many instances, Phase 1 clinical evaluation has the potential to demonstrate whether there will be product differentiation. Potential advantages of our DCE Platform include the following:

- Improved metabolic profile. An improved metabolic profile may potentially reduce or eliminate unwanted side effects or undesirable drug interactions or increase efficacy. Metabolic profile refers to the relative amounts and exposure profile of the parent drug and its metabolites in the body.

- Increased half-life. A longer half-life may decrease the number of doses that a patient is required to take per day or provide more consistent exposure of the compound in comparison to the corresponding non-deuterated compound. Half-life is a measure of how long it takes for the body to clear half of the dose of the drug.

- Avoidance of undesirable metabolism: By avoiding first pass metabolism, we may be able to improve oral bioavailability, which could potentially lead to better efficacy at a lower dose of drug. First pass metabolism is metabolism that occurs before the drug reaches the circulatory system.

OUR PRODUCT CANDIDATES

Our pipeline is focused on leveraging our deuterium expertise and proprietary product platform to develop novel medications designed to enhance patient outcomes in diverse therapeutic areas including genetic disease, inflammatory disease and neurologic disorders. The discussion below highlights our current clinical programs including those being developed by our collaborators.

CTP-656

Background on Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide. There is no known cure for cystic fibrosis. The median predicted survival age is close to 40 years and nearly half of the cystic fibrosis population is 18 or older. Cystic fibrosis is caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator protein, or CFTR, a chloride channel that regulates the movement of salt and water into and out of cells. Children who develop cystic fibrosis inherit two defective CFTR genes, one from each parent, which are referred to as alleles. There are more than 1,900 known mutations in the CFTR gene, some of which result in cystic fibrosis, including the most prevalent F508del mutation and the less prevalent G551D gating mutation. In the United States, it is estimated that approximately 85% of individuals with cystic fibrosis have at least one F508del mutation and approximately 4.4% of people with cystic fibrosis have a G551D gating mutation. Each mutation causes a different defect in the CFTR protein. When there is a defect caused by the G551D gating mutation, the defective CFTR protein reaches the surface of a cell but does not efficiently transport chloride ions across the cell membrane. The F508del mutation results in a different defect that largely prevents the CFTR protein from reaching the cell surface and also impairs its ability to transport chloride ions.

Defective CFTR results in decreased chloride secretion and reduced hydration of the mucus layer leading to the buildup of thick mucus in the lungs and other vital organs. Lung disease, the most critical manifestation of cystic fibrosis, is characterized by airway obstruction, infection and inflammation, such that more than 90% of all cystic fibrosis patients die of lung disease. Cystic fibrosis patients typically require lifelong treatment, with multiple daily medications, in many cases hospitalization due to lung infections, and potentially lung transplantation.

Ivacaftor (Kalydeco®) is a drug marketed by Vertex Pharmaceuticals, Inc., or Vertex, and initially approved for patients with the G551D gating mutation. The label has been expanded to include patients with certain other mutations. Ivacaftor is a CFTR potentiator, which keeps the CFTR protein channels on the cell surface open more often, to increase the flow of salt and water into and out of the cell. Vertex has also developed Orkambi®, a combination of lumacaftor and ivacaftor, which is marketed for patients with two F508del mutations.

CTP-656 Opportunity

CTP-656 is a novel, next generation potentiator that we are initially developing for the treatment of cystic fibrosis in patients who have gating mutations, including the G551D mutation. CTP-656 was discovered by applying our deuterium chemistry technology to modify ivacaftor, which is the current standard of care for this population. Due to its differentiated pharmacokinetic profile, CTP-656 has the potential to offer a greater therapeutic benefit relative to ivacaftor for this patient population. The potential benefits of CTP-656 include improved efficacy due to better treatment adherence, as a result of once-daily dosing and enhanced exposure to the parent drug, which is more active than the metabolites; and fewer drug-drug interactions.

CTP-656 also has the potential to be a key component of combination therapies that enable the treatment of patients having many other CFTR mutations. To advance combination therapies of CTP-656, we intend to collaborate with companies who are focused on developing drugs that target other mechanisms of action and that we believe may be suitable to combine with CTP-656.

Clinical Development of CTP-656

In the third quarter of 2015, we completed a single ascending dose Phase 1 trial in healthy volunteers which included a comparison of CTP-656 with a single dose of Kalydeco. The single ascending dose Phase 1 clinical trial was conducted in 10 healthy volunteers and evaluated three doses (75, 150 and 300 mg) of CTP-656 as an aqueous suspension and a single dose 150 mg tablet of Kalydeco in one period. The single ascending dose findings support once-daily administration of CTP-656 based on a half-life in the range of 14 to 17 hours. In this trial, CTP-656 also demonstrated a linear dose response. CTP-656 was well-tolerated across all dose groups. There were no serious adverse events reported in subjects who received CTP-656.

Comparison of CTP-656 single dose pharmacokinetic profiles against Kalydeco®

In the single dose crossover comparison of an aqueous suspension of 150 mg of CTP-656 to a 150 mg solid dose of Kalydeco, nine subjects completed the Phase 1 trial, and CTP-656 demonstrated a superior pharmacokinetic profile. CTP-656 demonstrated a reduced rate of clearance, longer half-life, and substantially increased exposure with greater plasma levels at 12

and 24 hours vs. Kalydeco. For CTP-656, there was greater plasma exposure of the parent drug relative to its less active metabolites. With Kalydeco, the less active metabolites were more prominent than the parent drug.

In November 2015, we initiated a multiple ascending dose Phase 1 clinical trial in healthy volunteers. The trial is being conducted in two parts and will enroll approximately 38 healthy volunteers to assess safety, tolerability and pharmacokinetics of CTP-656 in a tablet formulation. The first part assessed the pharmacokinetic properties of a single dose tablet formulation of 150 mg of CTP-656 versus the 150 mg commercial tablet formulation of Kalydeco in 8 healthy volunteers following a high-fat meal. The second part will assess three doses of CTP-656, starting at 75 mg and up to 225 mg daily for seven days compared to placebo, again following a high-fat meal.

In February 2016, we announced results from Part 1 of the multiple ascending dose trial with a tablet formulation of CTP-656. The data from this trial was consistent with results from the previously completed single ascending dose trial, in which an aqueous suspension of CTP-656 demonstrated superior pharmacokinetic properties compared to Kalydeco. In this trial, CTP-656 tablets demonstrated a reduced rate of clearance, longer half-life, substantially increased exposure and greater plasma levels at 24 hours compared to Kalydeco. With both the solid dose and aqueous suspension formulations, the overall metabolite exposure profile of CTP-656 differed from that of Kalydeco. After administration of CTP-656, there was greater plasma exposure of the more active parent drug relative to less-active metabolites, whereas with Kalydeco there was greater plasma exposure of the less-active metabolites.

Top-line data from Part 2 of the Phase 1 multiple ascending trial and a food effect trial are expected in the second quarter of 2016. We also plan to commence a Phase 2 clinical trial with CTP-656 in patients with cystic fibrosis associated with gating mutations in the second half of 2016.

Collaboration Product Candidates-Development Programs

We have entered into several collaborative arrangements with companies to develop deuterium-modified versions of their marketed products. The deuterium product candidates may be developed for an existing indication or in new indications.

AVP-786

In February 2012, we granted Avanir Pharmaceuticals, Inc., or Avanir, an exclusive worldwide license to develop and commercialize deuterated dextromethorphan analogs. Subsequent to our agreement, Avanir was acquired by Otsuka Pharmaceutical Co., Ltd. and is now a wholly owned subsidiary of Otsuka America, Inc.

Avanir is developing AVP-786, which is a combination of a deuterated dextromethorphan analog and a low dose of quinidine. Avanir is conducting several Phase 2 and Phase 3 clinical trials to evaluate AVP-786 for the treatment of neurologic and psychiatric disorders.

- In November 2015, Avanir announced the initiation of the Phase 3 clinical program to evaluate the safety and efficacy of AVP-786 for the treatment of agitation associated with Alzheimer's disease. It expects to enroll approximately 700 patients in two Phase 3 trials. The Phase 3 trials are expected to be completed in the third quarter of 2018.

- In August 2014, Avanir initiated a Phase 2 randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of AVP-786 as an adjunctive treatment in patients with major depressive disorder who have had an inadequate response to antidepressant treatment. This trial is expected to be completed in the second quarter of 2016.

- In September 2015, Avanir initiated a Phase 2 clinical trial to evaluate the safety and efficacy of AVP-786 as an adjunctive treatment for patients with residual schizophrenia. This trial is expected to be completed in the third quarter of 2017.

CTP-730

In April 2013, we entered into a strategic worldwide collaboration with Celgene Pharmaceuticals, Inc., Celgene International Sarl and Celgene Corporation, together referred to as Celgene, related to certain deuterium-substituted compounds for the treatment of inflammation or cancer. While the collaboration has the potential to encompass multiple programs, it is initially focused on one program, CTP-730.

CTP-730 is a deuterated analog of apremilast, which is marketed by Celgene for the treatment of certain types of psoriasis and psoriatic arthritis. We have completed the Phase 1 clinical evaluation of CTP-730. Once daily dosing of 50 mg of CTP-730 administered for seven days in the Phase 1 clinical trial demonstrated similar steady state exposure to historical data for 30 mg

of apremilast twice daily. Treatment with CTP-730 was generally well-tolerated and no serious adverse events were observed. Celgene is responsible for any development of CTP-730 beyond the completed Phase 1 clinical trials. Celgene is assessing the path forward for CTP-730, however, CTP-730 has not advanced into new trials at this time.

JZP-386

In February 2013, we licensed the commercial rights to deuterated analogs of sodium oxybate, including JZP-386, to Jazz Pharmaceuticals under an exclusive worldwide license agreement. Sodium oxybate is the active ingredient in Xyrem®, marketed in the United States by Jazz Pharmaceuticals to treat two of the key symptoms of narcolepsy, excessive daytime sleepiness and cataplexy.

JZP-386 is being developed for the potential treatment of patients with narcolepsy. In May 2015, we and Jazz Pharmaceuticals announced the completion of a Phase 1 clinical study. Clinical data from this Phase 1 study demonstrated that JZP-386 provided favorable deuterium-related effects, including higher serum concentrations and correspondingly increased PD effects at clinically relevant time points compared to Xyrem® (sodium oxybate) oral solution. The safety profile of JZP-386 was similar to that observed with Xyrem. Jazz Pharmaceuticals is responsible for any further development of JZP-386.

INTELLECTUAL PROPERTY

We protect our product candidates through the use of patents, trade secrets and careful monitoring of our proprietary know-how. Our patents and patent applications, if they issue as patents, for our lead programs expire between 2028 and 2034. The expected expiration dates are before any patent term extension to which we may be entitled under the Hatch-Waxman Act or equivalent laws in other jurisdictions where we have issued patents.

AVP-786

We hold U.S. patents and pending applications covering the composition of matter and methods of use of the deuterated dextromethorphan analog, as well as a U.S. patent application covering methods of use of certain other dextromethorphan compounds. These patents and patent applications are expected to expire between 2028 and 2030. We have corresponding patents and patent applications in Europe and Japan that are expected to expire in 2028. We have granted exclusive licenses under these patent rights to Avanir.

CTP-656

We hold U.S. patents covering the composition of matter of deuterated analogs of ivacaftor and a corresponding U.S. patent application. The patents and the patent application are expected to expire in 2032. We have corresponding patent applications in Europe and Japan that are expected to expire in 2032. We have retained all of the CTP-656 patent rights.

JZP-386

We hold a U.S. patent, as well as a corresponding U.S. patent application, covering the composition of matter of deuterated analogs of sodium oxybate, including JZP-386, and methods of using them for treating certain diseases and disorders, including narcolepsy. This patent and patent application are expected to expire in 2030. We hold a corresponding European patent that is expected to expire in 2030. We also have a U.S. patent covering methods of use of JZP-386 for treating certain diseases and disorders, including narcolepsy, as well as patent applications in the United States, Europe and Japan, covering the composition of matter and methods of use of JZP-386, that are expected to expire in 2032. We have granted exclusive licenses under these patent rights to Jazz Pharmaceuticals.

CTP-730

We hold U.S. patents and a U.S. patent application covering the composition of matter of CTP-730. The patents and the patent application are expected to expire in 2030. We also hold corresponding patents in Europe and Japan that are expected to expire in 2030. We have granted exclusive licenses under these patent rights to Celgene.

Other Product Candidates

We also have patent portfolios that are related to a number of other programs. These patent portfolios are wholly owned by us. These include issued patents or patent applications that claim deuterated analogs of more than 90 non-deuterated drugs and drug candidates.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In the United States and other countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

Under U.S. patent law, the patent term may be extended by patent term adjustment due to certain failures of the U.S. Patent and Trademark Office to act in a timely manner. The patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-U.S. jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents that we believe are eligible for such extension. We also intend to seek patent term extensions in other jurisdictions where these are available. However, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secrets and careful monitoring of our proprietary know-how to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, including our DCE Platform, such as:

- our methods of evaluating candidate compounds for deuteration;
- our bioanalytical methods for identifying and measuring metabolites formed by the in vitro and in vivo metabolism of deuterated compounds;
- our analytical methods for evaluating how selective deuterium substitution affects different pharmacokinetic and metabolic parameters in vitro and in vivo systems; and
- our methods to determine the degree of deuterium substitution in compounds we manufacture.

MANUFACTURING AND SUPPLY

We currently rely, and expect to continue to rely, on third parties for the manufacture of product candidates for our clinical trials. We obtain these manufacturing services, including both the manufacture of the active pharmaceutical ingredients and finished drug product, on a purchase order basis and have not entered into long-term contracts with any of these third party manufacturers. We expect to rely on third parties for commercial manufacturing for any of our product candidates that receive marketing approval.

We have successfully transferred the methods we use in our internal manufacturing to our third party manufacturers, allowing them to produce multi-kilogram quantities of clinical trial materials with similar efficiency as we manufacture compounds internally. If any of our third party manufacturers should become unavailable to us for any reason, we believe that there are a number of potential replacements, although we might incur some delay in identifying and qualifying such replacements.

We believe that all of the deuterium that we use in manufacturing our product candidates is currently derived, directly or indirectly, from deuterium oxide. For most of our deuterium supply we rely on bulk supplies of deuterium oxide, which we currently source from multiple suppliers, including two located in North America, one of which is in the United States. In order to internationally transport any deuterium oxide that we purchase from foreign suppliers, we, or our U.S. supplier, may be required to obtain an export license from the country of origin and we may be required to

obtain an International Import Certificate from the country of destination. We are also generally required to obtain an export license from the Nuclear Regulatory Commission before shipping deuterium oxide from the United States to any contract manufacturer in another country. Each of these documents specifies the maximum amount of deuterium oxide that we, or our suppliers, are permitted to either import or export. In particular, in order to obtain additional supplies of deuterium oxide from one of the foreign suppliers from which we have previously purchased deuterium oxide, the supplier will be required to obtain an additional export license

from the country of origin and, as part of the export license application process, we may be required to obtain a U.S. import certificate. While we and our suppliers have obtained similar licenses and certificates in the past, we or our suppliers may not be able to obtain them in the future in a timely manner or at all.

Certain of our manufacturing processes for our product candidates incorporate deuterium by using deuterated chemical intermediates or reagents that are derived from deuterium oxide. For the deuterated chemical intermediates and reagents, we are not subject to the license requirements applicable to deuterium oxide. However, the manufacturer of the deuterated chemical intermediate or reagent may themselves be required to obtain deuterium oxide under applicable licensing requirements. Most of the manufacturers of these deuterated chemical intermediates and reagents are not located in countries that produce bulk quantities of deuterium oxide. Therefore, our ability to source these deuterated chemical intermediates or reagents will depend on the ability of these manufacturers to obtain deuterium oxide from other countries.

We purchase our raw materials on a purchase order basis and have not entered into long-term contracts with any of these third party suppliers. We believe that the raw materials for our product candidates are readily available and that the cost of manufacturing for our product candidates will not preclude us from selling them profitably, if approved for sale.

COMMERCIALIZATION

We have not yet established a sales, marketing or product distribution infrastructure. We plan to use a combination of third party collaboration, licensing and distribution arrangements and a focused in-house commercialization capability to sell any of our products that receive marketing approval. With respect to the United States, we plan to seek to retain full commercialization rights for products that we can commercialize with a specialized sales force and to retain co-promotion or similar rights when feasible in indications requiring a larger commercial infrastructure. We plan to collaborate with third parties for commercialization in the United States of any products that require a large sales, marketing and product distribution infrastructure. We also plan to collaborate with third parties for commercialization outside the United States.

We plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. We expect the responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with thought leaders in relevant fields of medicine.

COMPETITION

The development and commercialization of new drug products is highly competitive. We expect that we, and our collaborators, will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to our product candidates that we, or they, may seek to develop or commercialize in the future. Specifically, there are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of neurologic disorders, inflammation, and cystic fibrosis, the key indications for our current research and development programs. Our competitors may succeed in developing, acquiring or licensing technologies and drug products that are more effective, have fewer or more tolerable side effects or are less costly than any product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we, or our collaborators, may develop. Our competitors also may obtain FDA or other marketing approval for their products before we, or our collaborators, are able to obtain approval for ours, which could result in our competitors establishing a strong market position before we, or our collaborators, are able to enter the market.

Many of our existing and potential future competitors have significantly greater financial resources and expertise in research and development, manufacturing, non-clinical testing, conducting clinical trials, obtaining marketing

approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Many pharmaceutical and biotechnology companies have begun to cover deuterated analogs of their product candidates in patent applications and may choose to develop these deuterated compounds. Some of these pharmaceutical and biotechnology companies may have significantly greater financial resources and expertise in research and development, manufacturing, non-clinical testing, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. In addition, we know of other companies that are broadly utilizing deuterium substitution for drug development, including Auspex Pharmaceuticals, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., and DeuteRx LLC. In some cases, these competitors may be interested in developing deuterated compounds that we may be interested in developing for ourselves. In addition, these competitors may enter into collaborative arrangements or business combinations that result in their ability to research and develop deuterated compounds more effectively than us. Our potential competitors also include academic institutions, government agencies and other public and private research organizations.

AVP-786

Avanir is developing AVP-786 for the treatment of agitation associated with Alzheimer's disease, major depressive disorder and for adjunctive treatment for residual schizophrenia. While there are product candidates in clinical development for Alzheimer's agitation, such as brexpiprazole in Phase 3 development by Otsuka, there are no approved treatments. There are marketed drugs for major depressive disorder or product candidates in clinical development for each indication.

CTP-656

We are initially developing CTP-656, a deuterated analog of ivacaftor, as a treatment for cystic fibrosis in individuals with gating mutations of the CFTR gene, including G551D. The current standard of care for this population is ivacaftor, which is marketed by Vertex Pharmaceuticals, Inc. under the name Kalydeco®. If CTP-656 receives marketing approval, it would compete with this product and may face competition from a number of other product candidates that are currently in clinical development, including additional candidates being developed by Vertex, among others.

JZP-386

JZP-386 is a deuterated analog of sodium oxybate, which is being developed for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The current standard of care is treatment with sodium oxybate, which is marketed by Jazz Pharmaceuticals, Inc., under the name Xyrem®. Flamel Technologies SA announced their intent to initiate Phase 3 clinical development for an extended release formulation of sodium oxybate for the treatment of narcolepsy.

CTP-730

CTP-730 is a deuterated analog of apremilast, which is a selective inhibitor of the enzyme phosphodiesterase 4 or PDE4. Apremilast is marketed by Celgene for the treatment of certain types of psoriasis and psoriatic arthritis. Apremilast is also being evaluated for its efficacy in other chronic inflammatory diseases for which a PDE4 inhibitor may be useful. If CTP-730 receives marketing approval, it may face competition with drugs having the same or different mechanisms of action.

GOVERNMENT REGULATIONS

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, sales, distribution, marketing, and import and export of pharmaceutical products. The processes for obtaining

regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under The Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of

government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which allows human clinical trials to begin unless the FDA objects within 30 days;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with the FDA's current Good Clinical Practices, or cGCPs, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA;
- satisfactory review of the NDA by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the drug product, and the active pharmaceutical ingredient or ingredients thereof, are produced to assess compliance with current good manufacturing practices and to assure that the facilities, methods and controls are adequate to ensure the product's identity, strength, quality and purity;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including REMS and post-approval studies required by the FDA.

Preclinical Studies and an IND

Preclinical studies can include in vitro and animal studies to assess the potential for adverse events and, in some cases, to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. Other studies include laboratory evaluation of the purity, stability and physical form of the manufactured drug substance or active pharmaceutical ingredient and the physical properties, stability and reproducibility of the formulated drug or drug product. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. Some preclinical testing, such as longer-term toxicity testing, animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Following commencement of a clinical trial under an IND, the FDA may place a clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or

otherwise satisfying the FDA that the investigation can proceed.

Human Clinical Studies in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with cGCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring

safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the NIH for public dissemination on their ClinicalTrials.gov website. Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

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| Phase 1: | The product candidate is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness. |
| Phase 2: | The product candidate is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and dosage for Phase 3 studies. |
| Phase 3: | The product candidate is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. |

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will often inspect one or more clinical sites in late-stage clinical trials to assure compliance with cGCP and the integrity of the clinical data submitted.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two adequate and well-controlled clinical trials which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or may rely on published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the applicant relies, as part of its application, on investigations made to show whether or not the drug is safe and effective for use "that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant 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 to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

If our partners submit NDAs for approval of deuterated analogs of marketed compounds for which they are the NDA holder, we believe that in certain cases the FDA may allow referencing of data from the non-deuterated compound in support of the application for approval of the deuterated product. Since this referencing by our partners would involve use of their own data and not require the use of another party's data, it would constitute a Section 505(b)(1) application.

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling,

among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding $2.1 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $104,000 per product and $554,600 per establishment. These fees are typically increased annually.

Under certain circumstances, the FDA will waive the application fee for the first human drug application that a small business, defined as a company with less than 500 employees, or its affiliate submits for review. An affiliate is defined as a business entity that has a relationship with a second business entity if one business entity controls, or has the power to control, the other business entity, or a third party controls, or has the power to control, both entities.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA 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 cGCP.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation 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 considers such recommendations carefully when making decisions.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based

on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

The product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the

results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety and effectiveness of drug products.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events or problems with manufacturing processes of unanticipated severity or frequency, 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 trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

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.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing

previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD. To reference that information, however, the ANDA applicant must demonstrate, and the FDA must conclude, that the generic drug does, in fact, perform in the same way as the RLD it purports to copy.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is “bioequivalent” to the innovator drug. Under the statute, a generic drug is

bioequivalent to a RLD if "the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the reference listed drug. . . ."

Upon approval of an ANDA, the FDA indicates that the generic product is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider the therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of a therapeutic equivalence rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of data exclusivity for new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity is a drug that contains no active moiety that has been previously approved by FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such new chemical entity exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five year new chemical entity exclusivity, an award of three year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product.

Hatch-Waxman Patent Certification and the 30 Month Stay

NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book

to the same extent that an ANDA applicant would. As a result, approval of a 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, a NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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 from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States 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 non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA 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 trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of 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 accept or approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Amendments). Those Amendments permit a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of a NDA, plus the time between the submission date of a NDA and ultimate approval. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain

approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial applications must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a drug under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state’s assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Data and Market Exclusivity in the European Union

In the European Union, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator’s data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator’s data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the drug if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels, for such products. The

process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged for medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. In order to secure coverage and reimbursement for any product that might be approved for sale, a

company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has also become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on 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 adversely affect our net revenue and results.

Outside of the United States, ensuring adequate coverage and payment for products remains challenging. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

As a result, the marketability of any product which receives regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products that receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements for any of our products.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

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the federal healthcare Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the False Claims Act, which imposes civil monetary penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes federal criminal and civil liability for, among other things, knowingly and willingly executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Regulation of Deuterium Oxide

We believe that all of the deuterium that we use in manufacturing our product candidates is currently derived, directly or indirectly, from deuterium oxide. For most of our deuterium supply we rely on bulk supplies of deuterium oxide, which we currently source from multiple suppliers, including two located in North America, one of which is located in the United States. In order to internationally transport any deuterium oxide that we purchase from foreign suppliers, we, or our U.S. supplier, may be required to obtain an export license from the country of origin and we may be required to obtain an International Import Certificate from the country of destination. We are also generally required to obtain an export license from the Nuclear Regulatory Commission before shipping deuterium oxide from the United States to any contract manufacturer in another country. Each of these documents specifies the maximum amount of deuterium oxide that we, or our suppliers, are permitted to either import or export. We have obtained a license from the Nuclear Regulatory Commission, or NRC, for the export of 20,000 kilograms of heavy water over the life of the license, which is valid until January 2019. We have applied for an additional export license from the NRC. In addition, in order to obtain additional supplies of deuterium oxide from one of the foreign suppliers from which we have previously purchased deuterium oxide, the supplier will be required to obtain an additional export license from the country of origin and, as part of the export license application process, we may be required to obtain a U.S. import certificate. While we and our suppliers have obtained similar licenses and certificates in the past, we or our suppliers may not be able to obtain them in the future in a timely manner or at all. We have not obtained an export license from the country in which our potential future foreign supplier is located. In addition, if any of our product candidates is approved by the FDA, then the FDA will also have regulatory jurisdiction over the manufacture and use of deuterium oxide in such product.

EMPLOYEES

As of December 31, 2015, we had 59 employees, 39 of whom were primarily engaged in research and product development activities. A total of 22 employees have Ph.D. degrees. None of our employees are represented by a labor union and we believe our relations with our employees are good.

FACILITIES

Our offices are located in Lexington, Massachusetts, consisting of approximately 50,000 square feet of leased office and laboratory space. The term of the lease expires in September 2018.

LEGAL PROCEEDINGS

We are not currently a party to any material legal proceedings.

AVAILABLE INFORMATION

We file reports and other information with the Securities and Exchange Commission, or SEC, as required by the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. You can find, copy and inspect information we file at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov.

We were incorporated under the laws of the State of Delaware on April 12, 2006 as Concert Pharmaceuticals, Inc. Our principal executive offices are located at 99 Hayden Avenue, Suite 500, Lexington, Massachusetts, 02421, and our telephone number is (781) 860-0045. Our Internet website is http://www.concertpharma.com. We make available free of charge through our website our Annual Report 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 Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors," as a source of information about us.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this Annual Report on Form 10-K by reference.

Item 1A. Risk Factors.

Our business is subject to numerous risks. The following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in this Annual Report on Form 10-K and other filings with the Securities and Exchange Commission, or the SEC, press releases, communications with investors and oral statements. Actual future results may differ materially from those anticipated in our forward-looking statements. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

RISKS RELATED TO OUR FINANCIAL POSITION AND NEED FOR ADDITIONAL CAPITAL

We have incurred significant losses since inception, expect to incur losses for at least the next several years and may never sustain profitability.

We have incurred significant annual net operating losses in every year since our inception, except for fiscal year 2015. Although we were profitable for fiscal year 2015, as a result of a one-time payment of $50.2 million that we received in June 2015 as a result of our patent assignment agreement with Auspex, we expect to incur significant annual net operating losses in future periods. As of December 31, 2015, we had an accumulated deficit of $121.2 million. We have not generated any revenues from product sales and have financed our operations to date primarily through the public offering of our common stock, private placements of our preferred stock, debt financings and funding from collaborations and patent assignment agreement. We have not completed development of any product candidate and have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical development programs. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

We anticipate that our expenses will increase substantially if and as we:

- continue to develop and conduct non-clinical studies and clinical trials with respect to our product candidates;
- seek to identify additional product candidates;
- in-license or acquire additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize various products for which we may obtain marketing approval;
- require the manufacture of larger quantities of product candidates for clinical development and potentially commercialization;
- maintain, expand and protect our intellectual property portfolio;
- hire additional personnel;
- add equipment and physical infrastructure to support our research and development; and
- continue to implement the infrastructure necessary to support our product development and help us comply with our obligations as a public company.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or one of our collaborators is, able to successfully commercialize one or more of our product candidates. This will require success in a range of challenging activities, including completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we, or our collaborators, may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. We, and our collaborators, may never succeed in these activities and, even if we do, or one of our collaborators does, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations. A decline in the value of our company could cause our stockholders to lose all

or part of their investments in us.

We have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

We began operations in April 2006. Our operations to date have been limited to financing and staffing our company, developing our technology and product candidates and establishing collaborations. We have not yet demonstrated an ability to successfully conduct an international multi-center clinical trial, conduct a large-scale pivotal clinical trial, obtain marketing approvals, manufacture product on a commercial scale or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Developing pharmaceutical products, including conducting non-clinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. We expect our expenses to increase in connection with our ongoing activities, particularly as we initiate new clinical trials of, initiate new research and non-clinical development efforts for and seek marketing approval for, our product candidates, or if we in-license or acquire product candidates. In addition, if we obtain marketing approval for any of our product candidates, we may incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing and distribution are not the responsibility of one of our collaborators. In particular, the costs that we may be required to incur for the manufacture of any product candidate that receives marketing approval may be substantial. To our knowledge, no deuterated drug has ever been successfully commercialized. Manufacturing a deuterated drug at commercial scale may require specialized facilities, processes and materials. Furthermore, we will continue to incur costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

In any event, our existing cash and cash equivalents and investments will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of any of our product candidates. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

Based on our current expectations, including with respect to our development plans, we believe our existing cash and cash equivalents and investments as of December 31, 2015 will enable us to fund our operating expenses and capital expenditure requirements into 2018. Our estimate as to how long we expect our existing cash and cash equivalents and investments to be able to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances could cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the progress, timing, costs and results of clinical trials of, and research and non-clinical development efforts for, our product candidates and potential product candidates, including current and future clinical trials;
- our current collaboration agreements and achievement of milestones under these agreements;
- our ability to enter into and the terms and timing of any additional collaborations, licensing, product acquisition or other arrangements that we may establish;
- the number of product candidates that we pursue and their development requirements;
- the outcome, timing and costs of seeking regulatory approvals;
- our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure;

- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the costs of operating as a public company.

Raising additional capital may cause dilution to our stockholders or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings and additional collaborations and licensing arrangements. We do not have any committed external source of funds, other than potential milestone payments and royalties under our collaborations with Celgene, Avanir and Jazz Pharmaceuticals, each of which is subject to the achievement of development, regulatory and/or sales-based milestones with respect to our product candidates. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, the ownership interests of our stockholders may be materially diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect the rights of our stockholders. In addition, debt financing, if available, would result in increased fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, that could adversely impact our ability to conduct our business.

If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Any future indebtedness could adversely affect our ability to operate our business.

We could in the future incur indebtedness containing financial obligations and restrictive covenants, which could have significant adverse consequences, including:

- requiring us to dedicate a portion of our cash resources to the payment of interest and principal, reducing money available to fund working capital, capital expenditures, product development and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- subjecting us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

Any financial obligations or restrictive covenants could negatively impact our ability to conduct our business.

RISKS RELATED TO THE DISCOVERY, DEVELOPMENT AND COMMERCIALIZATION OF OUR PRODUCT CANDIDATES

Our approach to the discovery and development of product candidates based on selective deuteration is unproven, and we do not know whether we will be able to develop any products of commercial value.

We are focused on discovering and developing novel small molecule drugs that have improved metabolic or pharmacokinetic characteristics as a result of our selective substitution of deuterium for hydrogen. We apply our proprietary platform to systematically identify approved drugs, advanced clinical candidates or previously studied compounds that we believe can be improved with deuterium substitution to provide better pharmacokinetic or metabolic properties and thereby enhance clinical safety, efficacy and convenience. To our knowledge, no deuterated drug has ever been approved for sale in the United States. While we believe that selective deuteration can produce compounds that possess favorable pharmaceutical properties, we have not yet succeeded and may not succeed in demonstrating efficacy and safety for any of our product candidates in pivotal clinical trials or in obtaining marketing approval thereafter.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome.

Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of drug development, including failure to demonstrate efficacy in a clinical trial or

across a broad population of patients, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the Food and Drug Administration, or FDA, or any comparable foreign regulatory authority that a drug product is not approvable. It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials, we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

While we believe that our DCE Platform may enable drug discovery and clinical development that is more efficient and less expensive than conventional small molecule drug research and development, we may not be able to realize the advantages that we expect. In addition, while a key element of our drug discovery and development strategy involves utilizing existing information regarding non-deuterated compounds to assist the discovery and development of deuterated analogs of those compounds, not all of the product candidates that we develop are based on drugs or drug candidates that progressed into advanced clinical development. Particularly in these situations, existing information regarding the corresponding non-deuterated compound may not be sufficient to mitigate drug development risks.

In addition to the risk of failure inherent in drug development, certain of the deuterated compounds that we, and our collaborators, are developing and may develop in the future may be particularly susceptible to failure to the extent they are based on compounds that others have previously studied or tested, but did not progress in development due to safety, tolerability or efficacy concerns or otherwise. Deuteration of these compounds may not be sufficient to overcome the problems experienced with the corresponding non-deuterated compound.

We may not be able to continue further clinical development of our wholly owned development programs, including CTP-656. If we are unable to develop, obtain marketing approval for or commercialize our wholly owned development programs, ourselves or through a collaboration, or experience significant delays in doing so, our business could be materially harmed.

We currently have no products approved for sale. The success of our wholly owned development programs will depend on several factors, including:

- in the case of CTP-656, our ability to enroll sufficient numbers of patients and in a timely manner to conduct our clinical trials;
- in the case of CTP-656, if we need to develop it in combination with other agents to maximize its therapeutic and sales potential, our ability to develop or license such combinations;
- in the case of CTP-499, our ability to find a suitable partner to continue development;
- successful completion of clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- the performance of our future collaborators, if any, for our wholly owned development programs;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- establishment of supply arrangements with third party raw materials suppliers and manufacturers;
- our ability to manufacture or arrange for the manufacture of our wholly owned development programs with sufficient quality and quantity to support clinical trials and potential future commercialization;
- establishment of arrangements with third party manufacturers to obtain finished drug products that are appropriately packaged for sale;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- amount of commercial sales, if and when approved;
- a continued acceptable safety profile of our wholly owned development programs following any marketing approval; and
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agreement by third party payors to reimburse patients for the costs of treatment with our products, and the terms of such reimbursement.

If we are unable to successfully develop, receive marketing approval for, and commercialize our wholly owned development programs, or experience delays as a result of any of these factors or otherwise, our business could be materially harmed.

If clinical trials of our product candidates fail to satisfactorily demonstrate safety and efficacy to the FDA and other regulators, we, or our collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.

We, or our collaborators, must complete non-clinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans in order to obtain marketing approval from regulatory authorities for the sale of our product candidates. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. Further, the outcome of non-clinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, non-clinical and clinical data are often susceptible to varying interpretations and analyses. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face similar setbacks.

Any inability to successfully complete non-clinical and clinical development could result in additional costs to us, or our collaborators, and impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if (1) we, or our collaborators, are required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we, or they, contemplate (2) we, or our collaborators, are unable to successfully complete clinical trials of our product candidates or other testing, (3) the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, or (4) there are unacceptable safety concerns associated with our product candidates, we, or our collaborators, in addition to incurring additional costs, may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

Even if we, or our collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

If we, or our collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential marketing approval or commercialization of our product candidates could be delayed or prevented.

We, or our collaborators, may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent marketing approval of our product candidates, including:

- clinical trials of our product candidates may produce unfavorable or inconclusive results;
- we, or our collaborators, may decide, or regulators may require us or them, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we, or our collaborators, anticipate, patient enrollment in these clinical trials may be slower than we, or our collaborators, anticipate or participants may drop out of these clinical trials at a higher rate than we, or our collaborators, anticipate;
- our third party contractors or those of our collaborators, including those manufacturing our product candidates or components or ingredients thereof or conducting clinical trials on our behalf or on behalf of our collaborators, may fail to comply with regulatory requirements or meet their contractual obligations to us or our collaborators in a timely manner or at all;
- regulators or institutional review boards may not authorize us, our collaborators or our or their investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we, or our collaborators, may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- patients that enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial, extend the clinical trial's duration or cause spurious results;
- investigators may provide inaccurate or false data, resulting in spurious clinical results, an inadequate data set or regulators' unwillingness to approve a product;

- regulators or institutional review boards may require that we, or our collaborators, or our or their investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our or our collaborators' clinical trial design or our or their interpretation of data from non-clinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may change their requirements for approvability for a given product or for an indication after we have initiated work based on their previous guidance;
- the supply or quality of raw materials or manufactured product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply;
- we, or our manufacturing vendors, may not produce, or may not consistently produce material that meets necessary specifications for commercialization;
- the FDA or comparable foreign regulatory authorities may determine that our, or our manufacturing vendors, manufacturing or quality control processes fail to meet their specifications or guidelines; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us, or our collaborators, will increase if we, or they, experience delays in testing or pursuing marketing approvals and we, or they, may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We, and our collaborators, do not know whether any non-clinical tests or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant non-clinical or clinical trial delays also could shorten any periods during which we, or our collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of our collaborators, to bring products to market before we, or our collaborators, do and impair our ability, or the ability of our collaborators, to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

If we, or our collaborators, experience delays or difficulties in the enrollment of patients in clinical trials, our, or their, receipt of necessary regulatory approvals could be delayed or prevented.

We, or our collaborators, may not be able to initiate or continue clinical trials for any of our product candidates if we, or they, are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials as required by the FDA or comparable foreign regulatory authorities, such as the European Medicines Agency. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial;
- access to relevant clinical trial sites;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating.

Our inability, or the inability of our collaborators, to enroll a sufficient number of patients for our, or their, clinical trials could result in significant delays or may require us or them to abandon one or more clinical trials altogether. Enrollment delays in our, or their, clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our, or our

collaborators', ability to commence sales of and generate revenues from our product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

We believe we, or our collaborators, may in some instances be able to secure clearances from the FDA or comparable foreign regulatory authorities to use expedited development pathways. However, if we or our collaborators are unable to obtain such clearances, we, or they, may be required to conduct additional non-clinical studies or clinical trials beyond those that we, or they, contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals.

The deuterated compounds that we produce and seek to develop can have similar pharmacological properties as their corresponding non-deuterated compounds. Therefore, we believe that we, or our collaborators, may, in some instances, be able to obtain clearance from the FDA or comparable foreign regulatory authorities to follow expedited development programs for some deuterated compounds that reference and rely on findings previously obtained from prior non-clinical studies or clinical trials of the corresponding non-deuterated compounds. For example, our collaborator Avanir reported in June 2013 that the FDA has agreed to an expedited development pathway for AVP-786, a product candidate Avanir is developing that includes our licensed deuterated dextromethorphan compound, permitting Avanir to reference data from its development of dextromethorphan and quinidine in its investigational new drug application, or IND, and any future new drug application, or NDA for AVP-786.

While we anticipate that following an expedited development pathway may be possible for some of our current and future product candidates, we cannot be certain that we, or our collaborators, will be able to secure clearance to follow such expedited development pathways from the FDA or comparable foreign regulatory authorities. In addition, if we follow, or one of our collaborators follows, such an expedited regulatory pathway and the FDA or comparable foreign regulatory authorities are not satisfied with the results of our having done so, such as might be the case if a deuterated compound is found to have undesirable side effects or other undesirable properties that were not anticipated based on the corresponding non-deuterated compound, the FDA or foreign regulatory authorities may be unwilling to grant clearance to follow expedited development pathways for other deuterated compounds.

Consequently, we, or our collaborators, may be required to pursue full development programs with respect to any product candidates that we, or they, previously anticipated would be able to follow an expedited development pathway, including conducting a full range of non-clinical and clinical studies to attempt to establish the safety and efficacy of these product candidates. A need to conduct a full range of development activities would significantly increase the costs of development and length of time required before we, or our collaborators, could seek marketing approval of such a product candidate as compared to the costs and timing that we or they anticipate. While we have been able to reference, for purposes of some of our IND-enabling studies, data generated during development of the corresponding non-deuterated compound, we have not ourselves obtained clearance from the FDA or any comparable foreign regulatory authority to reference such data in connection with more advanced stages of development.

Serious adverse events, undesirable side effects or other unexpected properties of our product candidates, including those that we have licensed to collaborators, may be identified during development that could delay or prevent the product candidate’s marketing approval.

All of our product candidates are in non-clinical and clinical development stages and their risk of failure is high. Serious adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, one of our collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. A dose of a deuterated compound could, in comparison to an equal dose of the corresponding non-deuterated compound, result in increased exposure levels, distribution and half-life in the body and alter the levels of particular metabolites that are present in the body. These changes may cause serious adverse events or undesirable side effects that we or our collaborators did not anticipate, whether based on the characteristics of the corresponding non-deuterated compound or otherwise. If any of our product candidates is associated with serious adverse events or undesirable side effects or have properties that are unexpected, we, or our collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the compound. In addition, unexpected adverse clinical effects of a deuterated

product candidate, including either those identified by us or deuterated analogs of approved drugs being developed by any third parties, may create general concerns regarding deuteration technology that could delay the development of our product candidates.

Even if one of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third party payors and others in the medical community necessary for commercial success and the market opportunity for the product candidate may be smaller than we estimate.

Even if one of our product candidates, including those licensed to our collaborators, is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable.

The degree of market acceptance of our product candidates, including those licensed to our collaborators, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential advantages of the product compared to alternative treatments;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy;
- limitations or warnings, including distribution or use restrictions or burdensome prescription requirements contained in the product's approved labeling;
- our ability, or the ability of our collaborators, to offer the product for sale at commercially acceptable prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- the strength of sales, marketing and distribution support;
- the approval of other new products for the same indications;
- changes in the standard of care for the targeted indications for the product;
- the timing of market introduction of our approved products as well as competitive products; and
- availability and amount of reimbursement from government payors, managed care plans and other third party payors.

The potential market opportunities for our product candidates are difficult to precisely estimate. Our estimates of the potential market opportunities are predicated on many assumptions including industry knowledge and publications, third party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the drug, or that of our collaborators, could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

- regulatory authorities may withdraw their approval of the drug or seize the drug;
- we, or our collaborators, may be required to recall the drug or change the way the drug is administered;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular drug, including the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- we, or our collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or our collaborators, could be sued and held liable for harm caused to patients; and

- the drug may become less competitive.

Any of these events could have a material and adverse effect on our operations and business and could adversely impact our stock price.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates that we develop if and when those product candidates are approved.

We do not have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We plan to use a combination of third party collaboration, licensing and distribution arrangements and a focused in-house commercialization capability to sell any products that receive marketing approval.

We generally plan to seek to retain full commercialization rights for the United States for products that we can commercialize with a specialized sales force and to retain co-promotion or similar rights for the United States when feasible in indications requiring a larger commercial infrastructure. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. This may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

We plan to collaborate with third parties for commercialization in the United States of any products that require a large sales, marketing and product distribution infrastructure. We also plan to commercialize our product candidates outside the United States through collaboration, licensing and distribution arrangements with third parties. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales and marketing capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

We face substantial competition from other pharmaceutical and biotechnology companies and our operating results may suffer if we fail to compete effectively.

The development and commercialization of new drug products is highly competitive. We expect that we, and our collaborators, will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to our product candidates that we, or they, may seek to develop or commercialize in the future. Specifically, there are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of neurologic disorders, cystic fibrosis and inflammation, the key indications for our development programs. Our competitors may succeed in developing, acquiring or licensing technologies and drug products that are more effective, have fewer or more tolerable side effects or are less costly than any product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive.

Avanir is developing AVP-786 for the treatment of agitation associated with Alzheimer's Disease, major depressive disorder and residual schizophrenia. There are marketed drugs for major depressive disorder and product candidates in clinical development for each indication.

We are initially developing CTP-656, a deuterated analog of ivacaftor, as a treatment for cystic fibrosis. The current standard of care for the treatment of cystic fibrosis in patients who have gating mutations is ivacaftor, which is marketed by Vertex

Pharmaceuticals, Inc. under the name Kalydeco®. If CTP-656 receives marketing approval, it would compete with this product and may face competition from a number of other product candidates that are currently in clinical development, including additional candidates being developed by Vertex, among others.

JZP-386 is being developed for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The current standard of care is treatment with sodium oxybate. In addition, Flamel Technologies is currently developing an extended release formulation of sodium oxybate for the treatment of narcolepsy.

CTP-730 is a PDE4 inhibitor that has potential for the treatment of inflammatory diseases. The non-deuterated drug apremilast is marketed for certain types of psoriasis and psoriatic arthritis. It is also being evaluated for efficacy in other chronic inflammatory diseases. If CTP-730 receives marketing approval, it may face competition from drugs with similar or different mechanisms of action.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we, or our collaborators, may develop. Our competitors also may obtain FDA or other marketing approval for their products before we, or our collaborators, are able to obtain approval for ours, which could result in our competitors establishing a strong market position before we, or our collaborators, are able to enter the market.

Many of our existing and potential future competitors have significantly greater financial resources and expertise in research and development, manufacturing, non-clinical testing, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We also face competition in the development of deuterated compounds.

Many pharmaceutical and biotechnology companies have begun to cover deuterated analogs of their product candidates in patent applications and may choose to develop these deuterated compounds. Some of these pharmaceutical and biotechnology companies may have significantly greater financial resources and expertise in research and development, manufacturing, non-clinical testing, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. In addition, we know of other companies that are broadly utilizing deuterium substitution for drug development, including Auspex Pharmaceuticals, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., and DeuteRx LLC. In some cases, these competitors may be interested in developing deuterated compounds that we may be interested in developing for ourselves. In addition, these competitors may enter into collaborative arrangements or business combinations that result in their ability to research and develop deuterated compounds more effectively than us. Our potential competitors also include academic institutions, government agencies and other public and private research organizations.

If our competitors in the development of deuterated compounds are able to grow their intellectual property estates and create new and successful deuterated compounds more effectively than us, our ability to identify additional compounds for non-clinical and clinical development and obtain product revenues in future periods could be compromised, which could result in significant harm to our operations and financial position.

If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a “reference listed drug” in the FDA’s publication, “Approved Drug Products with Therapeutic Equivalence Evaluations.” Manufacturers may seek approval of generic versions of reference listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may

be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction

of a generic drug, a significant percentage of the sales of any branded product or reference listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference listed drug. While we believe that our product candidates contain active ingredients that would be treated as new chemical entities by the FDA and, therefore, if approved, should be afforded five years of data exclusivity, the FDA may disagree with that conclusion and may approve generic products after a period that is less than five years. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates.

To the extent we, or our collaborators, market products that are deuterated analogs of generic drugs that are approved or will be approved while we market our products, our products will likely compete against these generic products and the sales of our products could be adversely affected.

We anticipate that some of the products that we, or our collaborators, may develop will be deuterated analogs of approved drugs that are or will then be available on a generic basis. In addition, if we develop a product that is a deuterated analog of a non-generic approved drug, the FDA or comparable foreign regulatory authorities may also approve generic versions of the corresponding non-deuterated drug. If approved, we expect that our deuterated products will compete against these generic non-deuterated compounds in the same indications. Efforts to educate the medical community and third party payors on the benefits of any product that we develop as compared to the corresponding non-deuterated compound, or generic versions of it, may require significant resources and may not be successful. If physicians, rightly or wrongly, do not believe that a product that we, or our collaborators, develop offers substantial advantages over the corresponding non-deuterated compound, or generic versions of the corresponding non-deuterated compound, or that the advantages offered by our product as compared to the corresponding non-deuterated compound, or its generic versions, are not sufficient to merit the increased price over the corresponding non-deuterated compound, or its generic versions, that we, or our collaborators, would seek, physicians might not prescribe that product. In addition, third party payors may refuse to provide reimbursement for a product that we, or our collaborators, develop when the corresponding non-deuterated compound, or generic versions of the corresponding non-deuterated compound, offer a cheaper alternative therapy in the same indication, or may otherwise encourage use of the corresponding non-deuterated compound, or generic versions of the corresponding non-deuterated compound, over our product, even if our product possesses favorable pharmaceutical properties.

Competition that our product candidates may face from any generic non-deuterated product on which our product candidate is based or a later-approved generic version of a branded non-deuterated product on which our product is based, could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates.

If we develop a deuterated analog of a drug with orphan disease exclusivity, we may be prevented from marketing our compound prior to the expiration of that exclusivity unless we can show that the deuterated analog is not the same drug for the same indication.

Under the Orphan Drug Act, if the FDA has granted a drug orphan disease exclusivity with respect to an orphan indication, which is generally defined as a disease or condition with a patient population of less than 200,000 patients in the United States annually, the FDA cannot approve a new drug application for the same product and for the same orphan indication until the end of the exclusivity period of seven years following approval of the orphan drug. If one of our deuterium-modified analogs is deemed by the FDA to be the same product for the same indication as a corresponding non-deuterium modified drug that has orphan drug exclusivity, we may be prevented from marketing

our drug during the exclusivity period.

Even if we, or our collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third party payor reimbursement practices or healthcare reform initiatives that could harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third party payors. Government authorities and third party payors, such as private health insurers and health maintenance organizations, decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and third party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of our collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of our collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or our collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If reimbursement is not available, or is available only to limited levels, we, or our collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or our collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments.

There is significant uncertainty related to third party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or our collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of our collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Third party payor coverage of newly approved drugs may be more limited than the indications for which the drugs are approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the drug and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies, requiring burdensome comparison studies with currently approved drugs and challenging the prices charged. We, and our collaborators, cannot be sure that coverage will be available for any product candidate that we, or they, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we, or our collaborators, obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

We may not be successful in our efforts to identify or discover additional potential product candidates.

A significant portion of our research involves the development of new deuterated compounds using our DCE Platform. These efforts may not be successful in creating compounds that have commercial value or therapeutic utility beyond the corresponding non-deuterated compound, or at all. Our research programs may initially show promise in

creating potential product candidates, yet fail to yield viable product candidates for clinical development for a number of reasons, including:

- deuterated analogs of existing non-deuterated compounds or newly designed deuterated compounds may not demonstrate satisfactory efficacy or other benefits, such as convenience of dosing, increased tolerability, enhanced formation of desirable active metabolites or reduced formation of toxic metabolites;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance; or

pharmaceutical and biotechnology companies have begun to claim deuterated analogs of their compounds in patent filings, resulting in otherwise promising deuterated product candidates already being covered by patents or patent applications.

If we are unable to identify suitable additional compounds for non-clinical and clinical development, our ability to develop product candidates and obtain product revenues in future periods could be compromised, which could result in significant harm to our financial position and adversely impact our stock price.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we or our collaborators commercially sell any product that we may or they may develop. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend litigation;
- distraction to our management diverting focus from business operations and strategy;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products that we may develop.

Although we maintain product liability insurance coverage, it may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we begin selling any product candidate that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could adversely affect our business, financial condition, results of operations and prospects.

JZP-386 is a deuterated analog of a Schedule I controlled substance and the active pharmaceutical ingredient will likely be classified as a Schedule I controlled substance and the drug product will likely be classified as a Schedule III controlled substance, which could substantially limit our, or our collaborator's, ability to obtain the quantities of JZP-386 needed to conduct clinical trials and the ability of our collaborator to market and sell JZP-386 if it receives marketing approval.

The placement of drugs or other substances into schedules under the Controlled Substances Act of 1970, or CSA, is based upon the substance’s medical use, potential for abuse and safety or dependence liability. Under the CSA, every person who manufactures, distributes, dispenses, imports or exports any controlled substance must register with the U.S. Drug Enforcement Agency, or DEA, unless exempt. Our product candidate JZP-386, which we have licensed to Jazz Pharmaceuticals, is a deuterated sodium oxybate analog. Sodium oxybate is regulated as a chemical by the DEA as a Schedule I controlled substance. Because of the Schedule I classification of sodium oxybate, JZP-386 is regulated by the DEA as a Schedule I controlled substance. As a result, we or Jazz Pharmaceuticals will be required to obtain a license to ship the chemical intermediate that we are using as the precursor to JZP-386, which may delay or prevent the manufacturing of JZP-386 for clinical trials.

Specifically, the DEA limits the quantity of certain Schedule I controlled substances that may be produced in the United States in any year through a quota system. If our contract manufacturers for JZP-386, or those for Jazz Pharmaceuticals, manufacture JZP-386 in the United States, they will be required to obtain separate DEA quotas to

supply us or Jazz Pharmaceuticals with JZP-386 for the conduct of clinical trials. Different, but potentially no less burdensome regulations, may apply if we or Jazz Pharmaceuticals choose to contract for the manufacture of JZP-386 outside of the United States.

The process of obtaining the quotas needed to conduct the planned clinical trials of JZP-386 may involve lengthy legal and other efforts and we or Jazz Pharmaceuticals, or suppliers or manufacturers for us or Jazz Pharmaceuticals, may not be able to obtain sufficient quotas from the DEA. If we or Jazz Pharmaceuticals, or suppliers or manufacturers for us or Jazz

Pharmaceuticals, cannot obtain the quotas that are needed on a timely basis, or at all, we and Jazz Pharmaceuticals may not be able to conduct, on a timely basis or at all, the clinical trials of JZP-386 that are planned, and our business, financial condition, results of operations and growth prospects could be adversely affected.

If JZP-386 is approved for marketing in the United States, we believe that the commercial drug containing JZP-386 will remain subject to the CSA as a Schedule III controlled substance. Those restrictions could limit the marketing and distribution of the commercial drug containing JZP-386.

In addition, failure to maintain compliance with applicable requirements under the CSA, particularly as manifested in loss or diversion of regulated substances, can result in enforcement action that could include civil penalties, refusal to renew registrations or quotas, revocation of registrations or quotas or criminal proceedings, any of which could have a material adverse effect on our business, results of operations and financial condition. Individual states also regulate controlled substances, and we and Jazz Pharmaceuticals, and contract manufacturers for us and Jazz Pharmaceuticals, will be subject to state regulation on distribution of these products.

RISKS RELATED TO OUR DEPENDENCE ON THIRD PARTIES

We depend on collaborations with third parties for the development and commercialization of some of our product candidates and expect to continue to do so in the future. Our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We have entered into collaborations with Celgene, Avanir and Jazz Pharmaceuticals for the development and commercialization of certain of our product candidates and expect to enter into additional collaborations in the future. We have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates and our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, our collaborators have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates pose a number of risks, including:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- product candidates developed in collaboration with us, including in particular product candidates based on deuteration of a collaborator's marketed drugs or advanced clinical candidates, may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
-

collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed to it by us.

We expect to seek to establish additional collaborations, and if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. We are seeking a collaborator for CTP-499 and may seek one or more collaborators for the development and commercialization of one or more of our product candidates. We do not currently intend to conduct further clinical development of CTP-499 for the treatment of diabetic nephropathy absent such a collaboration.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidate from its corresponding non-deuterated analog, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. We are also restricted under the terms of certain of our existing collaboration agreements from entering into collaborations regarding or otherwise developing specified compounds that are similar to the compounds that are subject to those agreements and collaboration agreements that we enter into in the future may contain further restrictions on our ability to enter into potential collaborations or to otherwise develop specified compounds.

We may not be able to negotiate collaborations for CTP-499 or our other product candidates on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to limit the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue. In cases where we seek a collaborator for a product compound that is a deuterated analog of a compound that has been previously developed, failure to enter into a collaboration with the developer of the corresponding non-deuterated compound may result in a loss of the potential to obtain clearance from the FDA to follow expedited development programs that reference and rely on findings previously obtained from the developer's prior non-clinical or clinical studies of the corresponding non-deuterated compound.

We rely on third parties to conduct our clinical trials and some aspects of our research and non-clinical testing. If they terminate their relationships with us or do not perform satisfactorily, our business may be materially harmed.

We do not independently conduct clinical trials of any of our product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct these clinical trials and expect to rely on these third parties to conduct clinical trials of any other product candidate that we develop. We also rely on third parties to conduct some aspects of our research and non-clinical testing and expect to rely on these third parties in the future. Any of these third parties may terminate their engagements with us under certain circumstances. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third parties on commercially reasonable terms or at

all. Switching to or adding additional third parties would involve additional cost and require management time and focus. In addition, there is a natural transition period when a new third party commences work, which could result in delays in our product development activities. Although we seek to carefully manage our relationships with our contract research organizations, any such challenges or delays could have a material adverse impact on our business, financial condition and prospects.

Our reliance on these third parties for clinical development activities limits our control over these activities but we remain responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and

scientific standards. For example, notwithstanding the obligations of a contract research organization for a trial of one of our product candidates, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as current Good Clinical Practices, or cGCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The FDA enforces these cGCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites and institutional review boards. If we or our third party contractors fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our product candidates, which would delay the marketing approval process. We cannot be certain that, upon inspection, the FDA will determine that any of our clinical trials comply with cGCPs.

Furthermore, these third parties are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time, skill and resources to our ongoing development programs. These contractors may also have relationships with other commercial entities, including our competitors, which could impede their ability to devote appropriate time to our clinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct their services in accordance with our contracts, regulatory requirements or our stated protocols, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. In such an event, our financial results and the commercial prospects for any product candidates that we seek to develop could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue.

We are also required to register clinical trials and post the results of completed clinical trials on a government-sponsored database, such as ClinicalTrials.gov, within certain timeframes. Failure to do so can result in the inability to report our clinical results in certain publications, fines, adverse publicity and civil and criminal sanctions.

Because there are limited sources of deuterium, we, and our collaborators, are exposed to a number of risks and uncertainties associated with our deuterium supply.

We believe that all of the deuterium that we use in manufacturing our product candidates is currently derived, directly or indirectly, from deuterium oxide. For most of our deuterium supply, we rely on bulk supplies of deuterium oxide which we currently source from multiple suppliers, including two located in North America, one of which is in the United States.

In order to internationally transport any deuterium oxide that we purchase from our current or potential future foreign suppliers, we, or our suppliers, may be required to obtain an export license from the country of origin and we may be required to obtain an International Import Certificate or other governmental approvals or assurances from the country of destination. We are also required to obtain an export license from the Nuclear Regulatory Commission before shipping deuterium oxide from the United States to any contract manufacturer in another country. Export licenses and certain other required documents may specify the maximum amount of deuterium oxide that we, or our suppliers, are permitted to either import or export. In order for us to obtain supplies of deuterium oxide from foreign suppliers, they may be required to obtain an export license from the country of origin and we may be required to obtain domestic governmental approvals or assurances. In addition, our current U.S. export licenses may be insufficient to meet our future requirements. We, or our suppliers, may not be able to obtain such licenses, approvals or assurances in a timely manner or at all.

Certain of our manufacturing processes for our product candidates incorporate deuterium by using deuterated chemical intermediates or reagents that are derived from deuterium oxide. For the deuterated chemical intermediates and reagents, we are not subject to the license requirements applicable to deuterium oxide; however the manufacturer

of the deuterated chemical intermediate or reagent may themselves be required to obtain deuterium oxide under applicable licensing requirements. Most of the manufacturers of these deuterated chemical intermediates and reagents are not located in countries that produce bulk quantities of deuterium oxide. Therefore, our ability to source these deuterated chemical intermediates will depend on the ability of these manufacturers to obtain deuterium oxide from other countries. In the future we may arrange for supplies of deuterated chemical intermediates or reagents from manufacturers located in countries from which they can source deuterium oxide in bulk. However, contract manufacturers in these countries may not represent a viable alternative to our current suppliers. We do not have long-term agreements with our suppliers of deuterated chemical intermediates or reagents and we obtain some of these deuterated chemical intermediates or reagents from single sources, putting us at risk of uncontrolled cost

increases or supply interruptions if we cannot establish alternative sourcing arrangements. Deuterated chemical intermediates may be expensive or difficult to obtain or may be produced by specialized techniques that are not widely practiced and we may not be able to enter into arrangements for larger scale supply of deuterated chemical intermediates on acceptable terms, or at all.

We estimate that our current sources of deuterium oxide will be sufficient to meet our anticipated requirements; however, we do not have long-term agreements with our current suppliers. If we are not able to establish or maintain supply arrangements, or any relevant foreign governments decide to withhold authorizations for the export of deuterium oxide that we seek, we may be unable to secure alternative sources. If we are unable to obtain sufficient supplies of deuterium oxide from our current suppliers or our potential future foreign supplier, we would be forced to either seek alternative suppliers of deuterium oxide, likely in other countries, or alternative sources of deuterium. Such alternative supplies may not be available to us on acceptable terms or at all.

If we are unable to obtain sufficient supplies of deuterium, our ability to produce our product candidates would be impeded and our business, financial condition and prospects could be harmed. In particular, certain of our manufacturing processes are projected to require particularly large quantities of deuterium for late-stage clinical trials and for commercialization. Consequently, any adverse impact on our ability to obtain deuterium oxide from our current suppliers, import deuterium oxide into the United States or export deuterium oxide to our contract manufacturers could have a particularly severe impact on our ability to develop or commercialize those product candidates.

Similarly, to develop and commercialize any of our licensed product candidates, our collaborators will need to obtain supplies of deuterium and will be subject to risks and requirements in connection with sourcing deuterium that are similar to the ones that we face. In addition, if any of our product candidates is approved by the FDA, then the FDA will also have regulatory jurisdiction over the manufacture and use of deuterium oxide and deuterated chemical intermediates or reagents in such products. Any adverse impact on our, or our collaborators', ability to obtain deuterium could delay or prevent the development or commercialization of our product candidates, which could have a material adverse effect on our business.

We contract with third parties for the manufacture and distribution of our product candidates for non-clinical and clinical testing and expect to continue to do so in connection with our future development and commercialization efforts. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We currently rely, and expect to continue to rely, on third party contractors to manufacture non-clinical and clinical supplies of our product candidates and to package, label and ship these supplies. We expect to rely on third party contractors to manufacture, package, label and distribute commercial quantities of any product candidate that we commercialize following approval for marketing by applicable regulatory authorities. Reliance on such third party contractors entails risks, including:

- manufacturing delays if our third party contractors give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreements between us and them;
- the possible termination or nonrenewal of agreements by our third party contractors at a time that is costly or inconvenient for us;
- the possible breach by the third party contractors of our agreements with them;
- possible theft of intellectual property or trade secrets;
- the failure of third party contractors to comply with applicable regulatory requirements;
- the possible mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified;
- possible contamination of our product during its manufacture;
- possible interruptions in our contractors' operations, including departure of key personnel, disruption due to merger and acquisitions activities or supply chain disruptions;

- the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

If any of our product candidates are approved by any regulatory agency, we plan to enter into agreements with third party contract manufacturers for the commercial production and distribution of those products. It may be difficult for us to reach agreement with a contract manufacturer on satisfactory terms or in a timely manner, especially if the manufacturer believes it is uniquely suited to use our deuterium chemistry manufacturing processes or that our deuterium chemistry manufacturing processes bear greater production risks than manufacture of non-deuterated compounds. In addition, we may face competition for access to manufacturing facilities as there are a limited number of contract manufacturers operating under current good

manufacturing practices, or cGMPs, that are capable of manufacturing our product candidates. Consequently, we may not be able to reach agreement with third party manufacturers on satisfactory terms, which could delay our commercialization efforts.

Third party manufacturers are required to comply with cGMPs and similar regulatory requirements outside the United States. Facilities used by our third party manufacturers must be approved by the FDA after we submit an NDA and before potential approval of the product candidate. Similar regulations apply to manufacturers of our product candidates for use or sale in foreign countries. We do not control the manufacturing process and are completely dependent on our third party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our product candidates. If our manufacturers cannot successfully manufacture material that conforms to the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure the applicable approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture, we may need to find alternative manufacturing facilities, which could result in delays in obtaining approval for the applicable product candidate.

In addition, our manufacturers are subject to ongoing periodic inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements both prior to and following the receipt of marketing approval for any of our product candidates. Some of these inspections may be unannounced. Failure by any of our manufacturers to comply with applicable cGMPs or other regulatory requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates and have a material adverse impact on our business, financial condition and results of operations.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

RISKS RELATED TO OUR INTELLECTUAL PROPERTY

If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our product candidates may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary product candidates. If we do not adequately protect our intellectual property, competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our novel product candidates that are important to our business. The patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Neither deuterium itself, nor the general concept of selective substitution of deuterium for hydrogen in existing compounds, are patentable; therefore we usually seek patents on a compound-by-compound basis or on a relatively narrow genus of compounds. We are not guaranteed that patents will issue protecting any particular deuterated compound for which we seek patent protection.

Our ability to obtain and maintain patent protection for our product candidates may be limited if disclosures of non-deuterated compounds are held to anticipate or make obvious claims of deuterated analogs of the same or similar compounds. In addition, several large pharmaceutical and biotechnology companies have begun to pursue patent protection for deuterated analogs of their products and product candidates, and may in the future obtain patent protection that covers deuterated analogs of those product candidates. If patents directed primarily to non-deuterated compounds are deemed to protect deuterated analogs of those compounds or patent claims on deuterated analogs of compounds become common in the biotechnology and pharmaceutical industries, these factors may limit, in part or in whole, our ability to seek and obtain patent protection for new product candidates based on deuterium modification of compounds. It may also limit in part or in whole, our ability to develop new product candidates based on deuterium modification of such compounds without obtaining a license from those patent holders.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain.

Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, we may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, reexamination, post grant review, inter partes review or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights.

Our pending and future patent applications may not result in patents being issued which protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad, including challenges through the U.S. Patent and Trademark Office post-grant review procedures. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.

While we have obtained composition of matter patents with respect to our most advanced product candidates, our DCE Platform is not patented. In seeking to develop and maintain a competitive position through our DCE Platform and as to other aspects of our business, we rely on trade secrets, including unpatented know-how, technology and other proprietary information. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our consultants, independent contractors, advisors, corporate collaborators, outside scientific collaborators, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our

proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

Third parties may sue us alleging that we are infringing their intellectual property rights, and such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Some of the non-deuterated compounds on which our current and future product candidates, including CTP-656, are based are products that are covered by issued patents or patent applications, the holders of which may attempt to assert claims against us. To date, we are not aware of any judicial decision holding that a patent that covers a non-deuterated compound should be construed to also cover deuterated analogs thereof, absent specific claims with respect to the deuterated analogs. However, any such judicial decision, or legal proceedings asserting such claims, could increase the likelihood of potential infringement claims being asserted against us. If any third party patents or patent applications are found to cover our product candidates or their methods of use, we may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

For example, CTP-656 is a deuterium-modified version of ivacaftor. Ivacaftor is marketed by Vertex under the name Kalydeco. Vertex currently has patents covering ivacaftor that may still exist if and when we receive marketing approval for CTP-656. If we have to defend ourselves in a patent infringement suit, we may incur significant expenses in doing so. Such litigation could delay our ability to market CTP-656 or prevent us from marketing CTP-656.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our products candidates, including interference proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. We may also assert that a patent claim for a corresponding non-deuterated compound does not cover our product. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party’s intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product and could be required to pay potentially significant damages. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, we could be found liable for monetary damages, including treble damages and attorneys’ fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not

have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

RISKS RELATED TO REGULATORY APPROVAL AND OTHER LEGAL COMPLIANCE MATTERS

Even if we complete the necessary non-clinical studies and clinical trials the marketing approval process is expensive, time consuming and uncertain and we may not obtain approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or our collaborators, will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of drug products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities, which regulations differ from country to country. Failure to obtain marketing approval for a product candidate in a given territory will prevent us and our collaborators from commercializing the product candidate in that territory. Our product candidates are in various stages of development and are subject to the risks of failure inherent in drug development. We, and our collaborators, have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction. We have limited experience in filing and supporting the applications necessary to gain marketing approvals.

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. This is the case even though the deuterated compounds that we produce and seek to develop can have similar pharmacological properties as their corresponding non-deuterated compounds. Even if, as a result of any such similarities, we, or our collaborators, obtain clearance from the FDA and other regulatory authorities to follow expedited development programs for some deuterated compounds that reference and rely on previous findings for non-deuterated compounds, the review and approval of our product candidates may still take a substantial period of time.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional non-clinical, clinical or other studies. In addition, varying interpretations of the data obtained from non-clinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or our collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability or that of our collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union and many other jurisdictions, we, or our collaborators, must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many territories outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that territory. Our products may not receive commercially feasible prices in any given

territory, or the price offered for our products in a territory may have an adverse effect on their prices in other territories if we were to accept. We, and our collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by

regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA.

Even if we, or our collaborators, obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we, or they, manufacture and market our products, which could materially impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We, and our collaborators, must therefore comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we and our collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, our collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we, or our collaborators, receive marketing approval for one or more of our product candidates, we, and our collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

If we, and our collaborators, are not able to comply with post-approval regulatory requirements, we, and our collaborators, could have the marketing approvals for our products withdrawn by regulatory authorities and our, or our collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any of our product candidates for which we, or our collaborators, obtain marketing approval in the future could be subject to post-marketing restrictions or withdrawal from the market and we, or our collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Any of our product candidates for which we, or our collaborators, obtain marketing approval in the future, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such product, among other things, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we, or our collaborators, do not market any of our product candidates for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and

abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products or their manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;

- restrictions on the indication, patient population, or other parameters for which the drug is approved;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Recently enacted and future legislation may increase the difficulty and cost for us and our collaborators to obtain marketing approval of and commercialize our product candidates and affect the prices we, or they, may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of our collaborators, to profitably sell any products for which we, or they, obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA only addresses drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA.

Among the provisions of the PPACA of potential importance to our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program new requirements to report financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other

things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and our collaborators to more stringent product labeling and post-marketing testing and other requirements.

Our future relationships with customers and third party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with third party payors and customers, if any, will subject us to broadly applicable fraud and abuse and other healthcare laws and regulations. The laws and regulations may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations in the U.S. include the following:

- Anti-Kickback Statute. The federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- False Claims Act. The federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim;
- HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services, and, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information;
- Transparency Requirements. Federal laws require applicable manufacturers of covered drugs to report payments and other transfers of value to physicians, other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians and other healthcare providers and their immediate family members;
- Controlled Substances Act. The CSA regulates the handling of controlled substances such as JZP-386; and
- Analogous State and Foreign Laws. Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws can apply to sales or marketing arrangements and claims involving healthcare items or services. In addition, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures and govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and require drug

manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that

may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts, which could adversely affect our business, financial condition, results of operations or prospects. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, such as the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

RISKS RELATED TO EMPLOYEE MATTERS AND MANAGING GROWTH

Our future success depends on our ability to retain our Chief Executive Officer and other key executives and to attract, retain and motivate qualified personnel.

Our industry has experienced a high rate of turnover of management personnel in recent years. Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the pharmaceutical research and development and business development expertise of Roger D. Tung, our President and Chief Executive Officer, as well as the other principal members of our management, scientific and development team. Although we have formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. In addition, although we maintain a key-man insurance policy with respect to Dr. Tung, we do not carry key-man insurance on any of our other executive officers or employees and may not carry any key-man insurance in the future.

If we lose one or more of our executive officers, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel on acceptable

terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors,

including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to develop and commercialize product candidates will be limited.

We expect to grow our organization and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As our pipeline grows and matures, we expect to experience significant growth in the number of our employees and the scope of our operations, including in the areas of drug manufacturing, regulatory affairs and sales, marketing and distribution. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities to devote time to managing these growth activities. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected expansion of our operations may lead to significant costs and may divert our business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

RISKS RELATED TO OUR COMMON STOCK

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.

The trading price of our comment stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- the success of existing or new competitive products or technologies;
- the timing, advancement of and results of non-clinical studies and clinical trials of any of our product candidates;
- commencement or termination of collaborations for our development programs;
- failure, delays, changes to or discontinuation of any of our development programs;
- regulatory or legal developments in the United States and other countries;
- regulatory actions relating to our product candidates;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- disclosures by our collaborators relating to our product candidates or competitive programs;
- merger or acquisition activity of our collaborators;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- receipt or expectation of receipt of revenues such as milestones, royalties, grants and license fees;
- sales of our common stock by us, our insiders or other stockholders;
- programmed trading based on technical stock chart or other inputs;
- portfolio restructuring by large shareholders;
- addition or removal of our stock from stock indices;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts that cover our stock;
- actions by short-sellers or supporters of our stock, including social media postings or reports;

- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

An active trading market for our common stock may not be sustained.

Although we have listed our common stock on The NASDAQ Global Market, an active trading market for our common stock may not be sustained. In the absence of an active trading market for our common stock, investors may not be able to sell their common stock at or above the price at which they acquired their shares or at the times that they would like to sell. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

We have broad discretion in the use of our cash reserves and may not use them effectively.

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

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and may remain an emerging growth company for up to five years. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, we are incurring and expect to incur additional significant legal, accounting and other expenses that we did not incur as a private company. We expect that these expenses will further increase after we are no longer an "emerging growth company." The Sarbanes-Oxley Act of 2002, or SOX, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We expect that we will need to hire additional personnel to comply with the requirements of being a public company, and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. We are currently evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and

governance practices.

Pursuant to SOX Section 404 we are required to evaluate the effectiveness of our internal control over financial reporting as of the end of each fiscal year and to report on this evaluation in our Annual Report on Form 10-K for the year. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial

reporting issued by our independent registered public accounting firm. We will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by SOX Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

A significant portion of our total outstanding shares may be sold into the market in the near future, which could cause the market price of our common stock to decline significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock.

In addition, as of February 23, 2016, there were 2,890,758 shares subject to outstanding options under our equity compensation plans, all of which shares we have registered under the Securities Act on a registration statement on Form S-8. These shares will be able to be freely sold in the public market upon exercise, as permitted by any applicable vesting requirements, except to the extent they are held by our affiliates, in which case such shares will become eligible for sale in the public market as permitted by Rule 144 under the Securities Act. Furthermore, as of February 23, 2016, there were 70,796 shares subject to an outstanding warrant to purchase common stock. These shares will become eligible for sale in the public market, to the extent such warrant is exercised, as permitted by Rule 144 under the Securities Act. Moreover, holders of a substantial portion of our outstanding common stock have rights, subject to conditions, to require us to file registration statements covering their shares or, along with the holder of our outstanding warrant to purchase common stock, to include their shares in registration statements that we may file for ourselves or other stockholders.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future, accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared or paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. Furthermore, any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

Our executive officers, directors and principal stockholders, if they choose to act together, have the ability to substantially influence all matters submitted to stockholders for approval.

As of December 31, 2015, our executive officers and directors, combined with our stockholders who owned more than 5% of our outstanding common stock, and all affiliates, in the aggregate, beneficially owned shares representing approximately 37.9% of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would substantially influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management or the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders

might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders.

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

The trading market for our common stock depends on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price may decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

ITEM 1B. Unresolved Staff Comments

None

ITEM 2. Properties

We lease our principal facilities, which consist of approximately 50,000 square feet of office, research and laboratory space located at 99 Hayden Avenue, Lexington, Massachusetts. The leases covering this space expire on September 30, 2018. We believe that our existing facilities are sufficient for our current needs for the foreseeable future.

ITEM 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

ITEM 4. Mine Safety Disclosures

Not applicable.

Part II

ITEM 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuers Purchases of Equity Securities

MARKET INFORMATION

Our common stock has been publicly traded on the NASDAQ Global Market under the symbol "CNCE" since February 13, 2014. Prior to that time, there was no public market for our common stock. Set forth below is the quarterly information with respect to the high and low prices for our common stock for the most recent fiscal year.

| | High | Low |
|---|---|---|
| Year Ended December 31, 2015 | | |
| First Quarter | $18.29 | $11.85 |
| Second Quarter | 17.84 | 13.11 |
| Third Quarter | 22.80 | 14.01 |
| Fourth Quarter | 25.04 | 18.47 |
| Year Ended December 31, 2014 | | |
| First Quarter | $16.26 | $11.42 |
| Second Quarter | 13.76 | 7.12 |
| Third Quarter | 15.19 | 7.50 |
| Fourth Quarter | 15.32 | 10.31 |

HOLDERS

As of January 31, 2016, there were 21 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

DIVIDENDS

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay any cash dividends to the holders of our common stock in the foreseeable future.

PERFORMANCE GRAPH

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the SEC for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, nor shall such information be incorporated by reference into any future filing under the Exchange Act or the Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our common stock to The NASDAQ Composite Index and to The NASDAQ Biotechnology Index from February 13, 2014 (the first date that shares of our common stock were publicly traded) through December 31, 2015. The comparison assumes $100 was invested after the market closed on February 13, 2014 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

PURCHASE OF EQUITY SECURITIES

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

USE OF PROCEEDS FROM REGISTERED SECURITIES

We effected the initial public offering of our common stock through a Registration Statement on Form S-1 (File No. 333-193335) that was declared effective by the SEC on February 12, 2014, and a registration statement on Form S-1 (File No. 333-193920) filed pursuant to Rule 462(b) of the Securities Act that became effective on February 12, 2014. The net

offering proceeds to us, after deducting underwriting discounts and commissions and offering expenses, were approximately $83.1 million.

As of January 31, 2016, we estimate that we have used all net proceeds of $83.1 million primarily to fund the development of CTP-354, CTP-656, to advance and expand the research and preclinical development of additional product candidates and for working capital, capital expenditures and other general corporate purposes. None of the net proceeds were paid directly or indirectly to directors or officers of ours or their associates or to persons owning 10 percent or more of our common stock or to any affiliate of ours, other than payments in the ordinary course of business to officers for salaries and to non-employee directors as compensation for board or board committee service. There has been no material change in our planned use of the balance of the net proceeds from the offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act.

ITEM 6. Selected Financial Data

The following tables set forth our selected consolidated financial data and has been derived from our audited consolidated financial statements. You should read the following selected consolidated financial data together with our consolidated financial statements and accompanying notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of the results that may be expected in any future period.

| | Years ended December 31, | | | | |
|---|---|---|---|---|---|
| (in thousands, except per share data) | 2015 | 2014 | 2013 | 2012 | 2011 |
| Results of Operations | | | | | |
| Total revenue | $66,729 | $8,576 | $25,408 | $12,849 | $19,467 |
| Operating expenses: | | | | | |
| Research and development | $28,885 | $27,474 | $21,790 | $24,193 | $23,436 |
| General and administrative | 13,056 | 11,700 | 8,028 | 7,266 | 7,377 |
| Total operating expenses | 41,941 | 39,174 | 29,818 | 31,459 | 30,813 |
| Income (Loss) from operations | 24,788 | (30,598) | (4,410) | (18,610) | (11,346) |
| Interest and other (expense) income, net | (185) | (1,101) | (1,646) | (1,834) | 26 |
| Provision for income taxes | 429 | — | — | — | — |
| Net income (loss) | $24,174 | $(31,699) | $(6,056) | $(20,444) | $(11,320) |
| Accretion on redeemable convertible preferred stock | — | (55) | (396) | (388) | (1,069) |
| Net income (loss) applicable to common stockholders - basic and diluted | $24,174 | $(31,754) | $(6,452) | $(20,832) | $(12,389) |
| Earnings Per Share | | | | | |
| Net income (loss) per share applicable to common stockholders - basic | $1.14 | $(2.00) | $(4.99) | $(16.15) | $(9.66) |
| Net income (loss) per share applicable to common stockholders - diluted | $1.09 | $(2.00) | $(4.99) | $(16.15) | $(9.66) |
| Weighted-average number of common shares used in net income (loss) per share applicable to common stockholders - basic | 21,152 | 15,842 | 1,292 | 1,290 | 1,283 |
| Weighted-average number of common shares used in net income (loss) per share applicable to common stockholders - diluted | 22,267 | 15,842 | 1,292 | 1,290 | 1,283 |
| Financial Condition | | | | | |
| Cash and cash equivalents | $92,510 | $13,396 | $9,638 | $7,490 | $22,949 |
| Investments, available for sale | 49,680 | 65,836 | 23,039 | 20,067 | 19,705 |
| Working capital | 137,481 | 63,102 | 18,128 | 20,940 | 33,861 |
| Total assets | 146,932 | 84,454 | 39,773 | 33,129 | 49,403 |
| Deferred revenue | 10,170 | 15,821 | 19,631 | 2,750 | 11,022 |
| Loan payable, net of discount | — | 7,101 | 14,919 | 19,731 | 7,135 |