CHIASMA, INC
Form 10-K
March 20, 2018
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2017

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: 001-37500

Chiasma, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**76-0722250**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**

460 Totten Pond Road, Suite 530

Waltham, MA	**02451**
(Address of Principal Executive Offices)	**(Zip Code)**

(617)-928-5300

(Registrant s Telephone Number, Including Area Code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value	**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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes No

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 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 No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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, a smaller reporting company, or an emerging growth company. See the definitions of large accelerated filer, accelerated filer smaller reporting company, and emerging growth company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	Smaller reporting company
		Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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

The aggregate market value of the registrant s common stock held by non-affiliates (without admitting that any person whose shares are not included in such calculation is an affiliate) as of June 30, 2017, was $26,748,236, based on the closing price of $1.45 of the registrant as reported on the NASDAQ Global Select Market on such date. As of March 8, 2018, there were 24,381,605 shares of common stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2017. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

CHIASMA, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2017

Table of Contents

		Page
PART I.		
Item 1.	Business	1
Item 1A.	Risk Factors	37
Item 1B.	Unresolved Staff Comments	88
Item 2.	Properties	88
Item 3.	Legal Proceedings	88
Item 4.	Mine Safety Disclosures	89
PART II.		
Item 5.	Market for Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	89
Item 6.	Selected Financial Data	92
Item 7.	Management s Discussion and Analysis of Financial Condition and Results of Operations	94
Item 7A.	Quantitative and Qualitative Disclosures about Market Risk	104
Item 8.	Financial Statements and Supplementary Data	104
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	104
Item 9A.	Controls and Procedures	104
Item 9B.	Other Information	105
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	105
Item 11.	Executive Compensation	105
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	106
Item 13.	Certain Relationships and Related Transactions and Director Independence	106
Item 14.	Principal Accountant Fees and Services	106
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	106
Item 16.	Form 10-K Summary	108
Signatures		109

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and is subject to the safe harbor created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as believes, expects, may, will, should, seek, intends, plans, estimates, projects, anticipates, or other comparable terms. These forward-looking statements involve risk and uncertainties. We cannot guarantee future results, levels of activity, performance or achievements, and you should not place undue reliance on our forward-looking statements. Our actual results may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those set forth in Item 1A. Risk Factors and elsewhere in this Annual Report. Except as may be required by law, we have no plans to update our forward-looking statements to reflect events or circumstances after the date of this Annual Report. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

Unless the content requires otherwise, references to Chiasma, the Company, we, our, and us, in this Annual Report refer to Chiasma, Inc. and its subsidiaries.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on improving the lives of patients who face challenges associated with their existing treatments for rare and serious chronic disease. Employing our proprietary Transient Permeability Enhancer, or TPE, technology platform, we seek to develop oral medications that are currently available only as injections. We are currently developing oral octreotide capsules, conditionally trade-named MYCAPSSA , our sole TPE platform-based clinical product candidate, in two Phase 3 clinical trials in adult patients for the treatment of acromegaly to potentially support regulatory approval in the United States and Europe. Acromegaly is a rare and debilitating condition that results in the body s production of excess growth hormone. Octreotide is an analog of somatostatin, a natural inhibitor of growth hormone secretion. We believe that octreotide capsules, if approved by regulatory authorities, will be the first somatostatin analog available for oral administration. Octreotide capsules have been granted orphan designation in the United States and the European Union for the treatment of acromegaly. The worldwide market for injectable somatostatin analogs is approximately $2.5 billion annually, of which we estimate approximately $775 million represents annual sales for the treatment of acromegaly. We retain worldwide rights to develop and commercialize octreotide capsules with no royalty obligations to third parties.

In September 2017, we initiated a third Phase 3 clinical trial for oral octreotide capsules for the maintenance therapy of adult patients with acromegaly following our agreement with the United States Food and Drug Administration, or the FDA, on the design of the trial, reached through a Special Protocol Assessment, or SPA, in August 2017. The trial, referred to as CHIASMA OPTIMAL, is a randomized, double-blind, placebo-controlled, nine-month trial expected to enroll 50 adult acromegaly patients designed to support regulatory approval of octreotide capsules in the United States. We expect to release top-line data from this trial by the end of 2019. We are also currently conducting an international Phase 3 clinical trial, referred to as MPOWERED, of oral octreotide capsules for the maintenance treatment of adult patients with acromegaly to support regulatory approval in Europe. The MPOWERED trial is a

global, randomized, open-label and active-controlled 15-month trial expected to enroll approximately 130 adult acromegaly patients, of which we expect to randomize at least 80 patients who are responders to octreotide capsules following a six-month run-in to either octreotide capsules or injectable somatostatin receptor ligands (octreotide or lanreotide), and then followed for an additional nine months. We currently expect to release top-line data from the MPOWERED trial in 2020.

Table of Contents

Octreotide capsules is the first somatostatin analog formulated for oral administration to complete a Phase 3 clinical trial. In November 2014, we completed a multinational open-label Phase 3 clinical trial of oral octreotide capsules for the treatment of acromegaly. Our original New Drug Application, or NDA, for octreotide capsules was submitted in June 2015 and accepted for filing by the FDA in August 2015. In April 2016, the FDA issued a complete response letter, or CRL, which indicated that the review of our application was complete and that our NDA was not ready for approval in its present form. In June 2016, we participated in an End of Review meeting with the FDA to discuss the concerns the FDA raised in the CRL. In its CRL, the FDA advised us that it did not believe our NDA had provided substantial evidence of efficacy to warrant approval, and advised us that we would need to conduct another clinical trial in order to overcome this deficiency. The FDA expressed concerns regarding certain aspects of our single-arm, open-label Phase 3 clinical trial and strongly recommended that we conduct a randomized, double-blind and controlled trial that enrolls patients from the United States and is of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. In addition, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval. While the FDA did not note any safety concerns related to octreotide capsules in the CRL, it subsequently indicated in the June 2016 End of Review meeting minutes that the size, duration, dropout rate and absence of a control group in our first Phase 3 trial were factors limiting an overall safety assessment. In the End of Review meeting minutes, the FDA reiterated its strong recommendation for a randomized, double-blind and controlled trial, and introduced the concept of a placebo control as a design element that could address some of the FDA s concerns.

In August 2017, we reached agreement with the FDA under a SPA of a new Phase 3 clinical trial of octreotide capsules in adult acromegaly patients, designed to address the concerns previously raised in the CRL, to potentially enable us to resubmit the NDA in order to secure regulatory approval of octreotide capsules in acromegaly. The trial, referred to as CHIASMA OPTIMAL (Octreotide capsules vs. Placebo Treatment In MultinationAL centers), which we initiated in September 2017, is a randomized, double-blind, placebo-controlled, nine-month clinical trial in 50 adult acromegaly patients (at least 20% of whom must be recruited from the United States) whose disease is biochemically controlled, based upon levels of insulin-like growth factor 1, or IGF-1, a byproduct of increased growth hormone, or GH, levels caused by acromegaly, on injectable somatostatin analogs at baseline (average IGF-1 £ 1.0 x upper limit of normal (ULN)). The patients must also have confirmed active acromegaly following their last surgical intervention based upon an elevated IGF-1 at that time of ³ 1.3 x ULN. The trial will be randomized on a 1:1 basis to octreotide capsules or placebo. Patients will be dose titrated from 40 mg per day to up to a maximum of 80 mg per day, equaling two capsules in the morning and two capsules in the evening. Patients meeting predefined biochemical failure withdrawal criteria in either treatment arm during the course of the trial will be considered treatment failures and revert to their original treatment of injections and will be monitored for the remainder of the trial. The primary endpoint of the study is the proportion of patients who maintain their biochemical response compared to placebo at the end of the nine-month double-blind, placebo controlled period as measured using the average of the last two IGF-1 levels £ 1.0 x ULN.

The hierarchical secondary endpoints that will be considered by the FDA in evaluating the totality of evidence for octreotide capsules treatment effect include:

Proportion of patients who maintain GH response at week 36 compared to screening;

Time to loss of response: IGF-1 > 1.0×ULN;

Time to loss of response: IGF-1 > 1.3×ULN;

Change from screening to end of treatment in mean GH; and

Change in IGF-1 from baseline to end of treatment.

The FDA required that the last two secondary endpoints be analyzed by comparing the octreotide capsules treatment arm to the placebo treatment arm at the end of the nine month, double-blind placebo controlled phase, including those patients that have been rescued by injectable somatostatin analogs. We estimate that as many as 90% or more, of the placebo-treated patients may require rescue therapy. As such, we have agreed to analyze the octreotide capsules treatment arm versus the placebo arm at the end of the study. We expect in particular the

Table of Contents

placebo arm will be highly populated with patients on injectable somatostatin analog rescue therapy. This analysis is referred to in statistical parlance as an ITT estimand. While we do not believe that superiority of Mycapssa will be demonstrated in these last two endpoints, we do believe that if we statistically achieve the primary efficacy endpoint, that is, the proportion of patients who maintain their biochemical response compared to placebo at the end of the nine-month double-blind placebo controlled period, and successfully achieve superiority in the higher-priority secondary endpoints, the totality of evidence supporting a robust treatment effect of octreotide capsules should be clear from the OPTIMAL trial. We anticipate that the FDA will review the totality of the data collected from the CHIASMA OPTIMAL trial, including both primary and secondary endpoints and whether the data collected are sufficiently robust to support the interpretability of these analyses, in determining whether to approve our NDA, if submitted, for the marketing and sale of octreotide capsules. There can be no assurance that the data collected from the CHIASMA OPTIMAL trial will be sufficient to support approval of our NDA, if submitted, for the marketing and sale of octreotide capsules. An open-label extension phase is planned following the nine-month study, which could enable patients who completed the randomized phase to continue receiving octreotide capsules and for us to collect long-term safety information. The results of the extension phase are not required as the basis for an efficacy claim.

In March 2016, in support of potential approval in Europe, we initiated an additional international Phase 3 clinical trial of octreotide capsules in acromegaly MPOWERED designed to show parallel comparative safety and effectiveness as required by the European Medicines Agency, or EMA. Assuming we receive favorable results from this second Phase 3 clinical trial in octreotide capsules, we expect to submit a Marketing Authorization Application, or MAA, to the EMA. Following the FDA s position that the MPOWERED clinical trial will not be sufficient to address the concerns in the CRL, in late 2016, we modified certain elements of the MPOWERED trial in an effort to preserve patients, sites and other resources necessary to conduct the CHIASMA OPTIMAL Phase 3 trial addressing the FDA s concerns and produce data packages suitable for submission in both the United States and the European Union. We now believe that approximately 130 patients will be required to enter the 6-month run-in phase of the trial in order to achieve the target 80 octreotide capsules responders randomized to the 9-month comparator phase of the 15-month trial, the number requested by the EMA. Based upon our first Phase 3 trial experience with octreotide capsules, we had estimated approximately 150 patients would be required to enter the run-in phase. Thus far, the aggregate number of patients withdrawing or not responding to octreotide capsules during the run-in phase is lower than originally expected. In September 2017, we announced that we had surpassed 50% patients randomized in the MPOWERED trial.

Importantly, we expect that the safety and efficacy data generated in all of our clinical trials of octreotide capsules, including our completed phase 3 clinical trial, the CHIASMA OPTIMAL clinical trial and the MPOWERED clinical trial, to the extent such data is available at the time of filing, will be integrated into our planned NDA, if resubmitted, and planned MAA filing. While CHIASMA OPTIMAL has been designed to address the FDA s concerns in the CRL and the MPOWERED trial design has been accepted by the EMA, our ultimate success in the regulatory review process of each planned application for marketing approval could be impacted by the trial results from any of our clinical trials.

Acromegaly is a condition caused by a benign tumor of the pituitary gland that releases excess GH, which in turn elevates IGF-1. These elevated hormone levels result in a number of painful and disfiguring symptoms, including some acute, such as headaches, joint pain and fatigue, and some long-term, such as enlarged hands, feet and internal organs, as well as altered facial features. If not treated promptly, acromegaly can lead to serious illness and is associated with premature death, primarily due to cardiovascular disease. According to data published by the Mayo Clinic in 2013, the mortality rate of people afflicted by acromegaly who go untreated is two to three times higher than that of the general population. Data from a published study presented at the Endocrine Society s Annual Meeting in 2015 suggest that the global prevalence of acromegaly may be between 85 and 118 cases per million people.

The current standard of care for patients diagnosed with acromegaly and not otherwise cured by surgical removal of the pituitary tumor consists of lifelong, once-monthly injections of an extended release somatostatin analog, primarily octreotide or lanreotide. These products contain a viscous formulation and are typically administered by a healthcare professional with large-gauge needles into the muscle or deep subcutaneously, that is, deeply

Table of Contents

under the skin. While injectable somatostatin analogs are generally effective at reducing GH and IGF-1 levels and therefore providing disease control, the injections are associated with significant limitations and patient burdens, including suboptimal symptom control, pain, injection-site reactions and other injection-related side effects, inconvenience, lost work days and emotional issues. Based on data reviewed in early 2016, we believe that approximately 8,000 adult acromegaly patients are chronically treated with somatostatin analogs in the United States, and that approximately 90% of these patients are managed by fewer than 1,000 accounts. Patients with acromegaly undergoing treatment in the United States are treated by endocrinologists at a small number of academic institutions with pituitary experts (pituitary centers), regional academic centers or hospital systems (regional referral centers) and some community endocrinologists.

We retain worldwide rights to develop and commercialize octreotide capsules with no royalty obligations to third parties. If approved, we may commercialize octreotide capsules ourselves in the United States and we plan to explore the strategic merits of collaboration opportunities for commercializing octreotide capsules in Europe and the rest of the world. Octreotide capsules are currently protected by issued patents lasting until at least 2029 in the United States, Europe, United Kingdom, Japan and several other jurisdictions, and by pending patent applications in additional jurisdictions that will last until 2029, if granted. We are also pursuing additional patent applications relating to particular uses, dosages and packaging for octreotide capsules.

Strategy

Our goal is to become a successful patient-focused biopharmaceutical company by developing and commercializing, ourselves or through others, octreotide capsules for acromegaly. Our strategy to pursue this goal includes the following elements:

Obtain U.S. regulatory approval of octreotide capsules for the treatment of acromegaly. We designed the CHIASMA OPTIMAL trial to address the concerns contained in the CRL and have secured agreement to the protocol and statistical analysis plan with the FDA under SPA procedures. We initiated this trial in September 2017 and currently expect to release top-line data from this trial by the end of 2019. Assuming favorable results, we expect to resubmit the NDA for FDA review to potentially secure approval in the United States for MYCAPPSA.

Obtain European regulatory approval of octreotide capsules for the treatment of acromegaly. To support approval in Europe, we initiated the Phase 3 MPOWERED clinical trial in March 2016, with a protocol that has been accepted by the EMA, to evaluate the comparative safety and efficacy of octreotide capsules in adult acromegaly patients. We currently expect to release top-line data from this trial in 2020, and assuming favorable results, we expect to submit our MAA to the EMA to potentially secure approval in Europe for MYCAPSSA.

Explore collaboration opportunities in Europe and the rest of the world for octreotide capsules in acromegaly. At the appropriate time, we intend to explore one or more collaborations to commercialize octreotide capsules in acromegaly outside of the United States. However, depending on our evaluation of the strategic merits of these collaboration opportunities, we may decide to retain commercial rights in key markets and undertake commercialization preparation and activities ourselves, if required regulatory approvals are obtained.

Our Product Candidate, Octreotide Capsules (MYCAPSSA) in Acromegaly

Product Candidate Overview

Octreotide capsules is a novel formulation of octreotide developed utilizing our TPE platform. We are developing octreotide capsules as a liquid-filled solid gelatin capsule formulation which is intended to be taken twice a day. We expect that acromegaly patients who are prescribed octreotide capsules, if approved, will receive a 28-day supply of pills, which may be stored at room temperature by the patient for up to one month. Based on the data from our previously completed clinical trials, not including data from our ongoing Phase 3 clinical trials, CHIASMA OPTIMAL or MPOWERED, we believe octreotide capsules have the potential to induce biochemical response (inhibition of GH and IGF-1) while improving symptoms and reducing the burden of disease and treatment in patients afflicted with acromegaly.

Table of Contents

Our product candidate, octreotide capsules, has completed one Phase 3 clinical trial for the treatment of acromegaly and 11 pharmacology and pharmacokinetic (PK) Phase 1 studies. In August 2015, our NDA for octreotide capsules as a maintenance therapy for acromegaly in the United States was accepted by the FDA for filing. In April 2016, the FDA issued a CRL to our NDA. In the CRL, the FDA advised us that it did not believe our NDA had provided substantial evidence of efficacy to warrant approval, and advised us that we would need to conduct another clinical trial in order to overcome this deficiency. The FDA expressed concerns regarding certain aspects of our single-arm, open-label Phase 3 clinical trial and strongly recommended that we conduct a randomized, double-blind and controlled trial that enrolls patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. In addition, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval. In June 2016, we participated in an End of Review meeting with the FDA where the FDA reiterated its concerns raised in the CRL. In the minutes from the End of Review Meeting, the FDA indicated that some of its concerns could potentially be addressed through a placebo-controlled study design. In December 2016, we were informed that the supplier referred to in the CRL had recently received its Establishment Inspection Report, or EIR, from the FDA. The receipt of the EIR is an indication that the FDA has concluded its inspection of the supplier and as of the date of its report considers outstanding deficiencies resolved. In September 2017, we initiated a Phase 3 clinical trial for oral octreotide capsules for the maintenance therapy of adult patients with acromegaly following our agreement with the FDA on the design of the trial, reached through a Special Protocol Assessment, or SPA, in August 2017. The trial, referred to as CHIASMA OPTIMAL, is a randomized, double-blind, placebo-controlled, nine-month trial expected to enroll 50 adult acromegaly patients designed to address the concerns raised in the CRL and support regulatory approval of octreotide capsules in the United States.

The EMA has advised us that a clinical trial demonstrating non-inferiority of octreotide capsules compared to injectable somatostatin analogs as active controls will be required prior to regulatory approval. We have agreed on the Phase 3 clinical trial protocol with the EMA and, in March 2016, we initiated an international Phase 3 clinical trial, referred to as MPOWERED, of oral octreotide capsules for the maintenance treatment of adult patients with acromegaly to support regulatory approval in Europe. Following the FDA s position that the MPOWERED clinical trial will not be sufficient to address the concerns in the CRL, we modified certain elements of the MPOWERED trial in an effort to preserve patients, sites and other resources necessary to conduct the Phase 3 CHIASMA OPTIMAL trial addressing the FDA s concerns and produce data packages that could be suitable for submission in both the United States and the European Union.

Overview of Acromegaly

Acromegaly results from the overproduction of GH, most often due to the growth of a benign tumor in the pituitary gland in middle-aged adults. GH, in turn, stimulates the production of IGF-1 in the liver which stimulates the growth of bones and other tissues. Progression of acromegaly can result in significant health problems such as hypertension, enlargement of the heart, or cardiomyopathy, sleep apnea, type-2 diabetes, and abnormal growths in the colon and uterus. Acromegaly is associated with a number of symptoms, some acute, such as headaches, joint pain and fatigue, and some long-term, such as enlarged hands, feet and internal organs, as well as altered facial features. Because acromegaly is uncommon and physical changes occur gradually, the condition is often not recognized immediately, sometimes not for years. If not treated promptly, acromegaly can lead to serious illness and is associated with premature death, primarily due to cardiovascular disease. However, both surgical and drug treatments are available for acromegaly that can reduce the risk of complications and premature death and significantly improve symptom control.

Surgery is often the first line of therapy for acromegaly and, in most cases, surgical removal of the pituitary tumor can result in normalization of GH and IGF-1 levels. In many other cases, however, the levels of GH remain elevated even after surgery due to residual tumor and many patients therefore also require a therapeutic intervention. The body s

natural inhibitor of excess GH secretion is somatostatin, a peptide hormone. Octreotide and lanreotide, analogs of somatostatin with a significantly longer half-life in the blood than natural somatostatin,

Table of Contents

have achieved widespread adoption by physicians treating patients afflicted with acromegaly. These somatostatin analogs are routinely administered by injection by a healthcare professional. If not administered with proper technique, the injection may not effectively deliver the medication. There is currently no oral formulation of a somatostatin analog on the market and none, we believe, in clinical development except octreotide capsules.

Incidence and Prevalence of Acromegaly and Current Treatment Landscape

There are an estimated 69,000 individuals with acromegaly worldwide. The U.S. National Institutes of Health, or NIH, estimates that there are roughly 20,000 individuals with acromegaly in the United States, based on its published prevalence of an estimated 60 cases per million. In 13 studies of acromegaly prevalence since 1980, an average of approximately 75 cases per million was determined, suggesting roughly 24,000 individuals with acromegaly in the United States. However, data presented at the Endocrine Society s Annual Meeting in 2015 suggest that pituitary tumors may be more prevalent than previously thought, and that the global prevalence of acromegaly may be higher, between 85 and 118 cases per million people. NIH also cites an annual incidence of three to four new cases per million each year.

According to publicly available financial reports, injectable forms of octreotide and lanreotide generate worldwide sales of approximately $2.5 billion annually for the treatment of acromegaly and neuroendocrine tumors, as well as some smaller indications. We believe approximately $775 million of this total represents the annual sales for the treatment of acromegaly. The great majority of these sales come from once-monthly long acting formulations that must be administered by intramuscular or deep subcutaneous injections with large-gauge needles. Although we are targeting acromegaly with octreotide capsules, we believe that this product candidate, if approved in acromegaly, has the potential to become a standard of care in other indications currently treated with injectable somatostatin analogs.

Current Therapeutic Options and Their Limitations

For acromegaly patients not cured by surgery, the current standard of care involves injectable somatostatin analogs. These therapies are associated with significant patient limitations and burdens. Currently, the first therapeutic treatment options are octreotide, marketed by Novartis AG, or Novartis, which is administered monthly and intramuscularly using a large gauge needle, and lanreotide, marketed by Ipsen SA, or Ipsen, another long-acting analog of somatostatin, which is administered monthly using a deep subcutaneous injection. Immediate release octreotide, while available, is more rarely used. For patients not controlled on these somatostatin analogs, the typical second line of treatment options (which may also be acceptably used as first line therapy) includes pegvisomant daily injections, marketed by Pfizer, Inc., or Pfizer, and pasireotide LAR, marketed by Novartis, which is another somatostatin analog administered monthly via intramuscular injection.

Current Injectable Treatment Options for Acromegaly

Product	Company	Route	Needle (length/gauge)	Status

Octreotide LAR	Novartis	Intramuscular	1.5 /19 or 20 G	Marketed
Lanreotide Depot	Ipsen	Deep Subcutaneous	0.79 /18 or 19 G	Marketed
Pasireotide LAR	Novartis	Intramuscular	1.5 /20 G	Marketed
Pegvisomant	Pfizer	Subcutaneous	1 /21-27 G	Marketed

Table of Contents

Injections of these somatostatin analogs present several issues related to patient comfort and convenience as well as breakthrough, or returning, symptoms of the disease near the end of the dosing cycle prior to the next scheduled injection. These issues include:

Suboptimal control. In a published patient-reported outcomes survey that we conducted in 195 acromegaly patients receiving injected somatostatin analogs, or our patient survey, 52% of patients reported that the treatment effects begin to wane near the end of the monthly cycle prior to the next injection, and 32% of controlled patients still experienced some symptoms.

Pain. Injections with somatostatin analogs require a large-gauge needle to slowly inject a viscous solution into the muscle or deep into subcutaneous tissue. Patients report these injections to be very painful. Often, this pain persists for several days after the injection. In our patient survey, 70% of patients said they experienced pain during the injection and approximately half of these patients experienced continuing pain days later.

Injection-site reactions. Patients frequently experience hardness, nodules and swelling at the site of the injection as well as bruising and inflammation.

Lack of convenience. The treatment effectiveness is dependent on proper delivery technique and thus the injections are typically administered by a healthcare professional. The monthly injection schedule for injectable somatostatin analogs and the associated travel to the healthcare provider is inconvenient for many patients.

Emotional impact. In our patient survey, 36% of patients said that they felt a loss of independence due to the requirement for chronic injections that typically require them to visit a healthcare professional.

Lost work days. In our patient survey, 16% of patients said that the treatment burden associated with the injectable therapies caused them to regularly miss work for injections. These patients missed an average of 11 days a year.

Since injectable somatostatin analogs are used in other diseases beyond acromegaly, these limitations and burdens are also associated with the treatment of the other indications that we may pursue with octreotide capsules, if approved in acromegaly.

Clinical Program for Octreotide Capsules in Acromegaly

United States Regulatory Pathway

We previously sought regulatory approval of octreotide capsules for the maintenance therapy of acromegaly in the United States utilizing the FDA s 505(b)(2) regulatory pathway. The 505(b)(2) pathway enables us to rely, in part, on the FDA s prior findings of safety and efficacy of an approved product, or published literature, in support of an NDA. In the case of octreotide capsules in acromegaly, the approved product to which our prior NDA submission referred is

the short-acting subcutaneous injectable formulation of octreotide that was the original product approved by the FDA before the long-acting formulation was developed. Since this formulation of octreotide was approved by the FDA in generic form and is therefore no longer proprietary, we are not aware of any third party from which we would be required to obtain any license or acquire any rights to commercialize octreotide capsules, if approved. As described in more detail below, we have conducted a series of Phase 1 clinical trials, including a trial to demonstrate that the systemic octreotide exposure from octreotide capsules, developed utilizing our TPE technology, is comparable to that of octreotide administered in the short-acting subcutaneous injectable formulation. We have also conducted a Phase 1 clinical trial to evaluate the bioactivity of octreotide capsules in healthy subjects, and a Phase 3 clinical trial to evaluate the safety and efficacy of octreotide capsules in patients with acromegaly, consisting of seven months of treatment plus an optional six-month extension phase.

In December 2014, we met with the FDA to discuss our clinical development of octreotide capsules, including the full 13-month data from our first Phase 3 clinical trial. At this meeting, the FDA advised us that it had not

Table of Contents

identified an issue that would preclude us from submitting an NDA for review. However, the FDA did advise us that interpreting efficacy from a voluntary long-term extension study is subject to limitations and therefore the data at the seven-month time point in our Phase 3 clinical trial would carry more weight in the efficacy evaluation than the extension data. The FDA has also informed us that, in its view, a single-arm study was not as informative as a controlled study, such as an active control trial using a non-inferiority design, and that the interpretability of the efficacy findings we submitted from our single-arm study, and whether these findings are robust enough to warrant approval, would be review issues as the FDA evaluated our NDA. In August 2015, our NDA for octreotide capsules for maintenance therapy in acromegaly was accepted for filing by the FDA.

In April 2016, the FDA issued a CRL to our NDA. In the CRL, the FDA advised us that it did not believe our NDA had provided substantial evidence of efficacy to warrant approval, and advised us that we would need to conduct another clinical trial in order to overcome this deficiency. The FDA expressed concerns regarding certain aspects of our single-arm, open-label Phase 3 clinical trial and strongly recommended that we conduct a randomized, double-blind and controlled trial that enrolls patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. In addition, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval. In December 2016, we were informed that the supplier had recently received its Establishment Inspection Report, or EIR, from the FDA. The receipt of the EIR is an indication that the FDA has concluded its inspection of the supplier and as of the date of its report considers outstanding deficiencies resolved. In June 2016, we participated in an End of Review meeting with the FDA where the FDA reiterated its concerns raised in the CRL. In the minutes from the End of Review Meeting, the FDA indicated that some of its concerns could potentially be addressed through a placebo-controlled study design.

Special Protocol Assessment and CHIASMA OPTIMAL Phase 3 Clinical Trial

In August 2017, we reached agreement with the FDA under a SPA of a new Phase 3 clinical trial of octreotide capsules in adult acromegaly patients, designed to address the concerns previously raised in the CRL, to potentially enable us to resubmit the NDA in order to seek regulatory approval of octreotide capsules in acromegaly. The CHIASMA OPTIMAL trial, which we initiated in September 2017, is a randomized, double-blind, placebo-controlled, nine-month clinical trial in 50 adult acromegaly patients (at least 20% of whom must be recruited from the United States) whose disease is biochemically controlled, based upon levels of insulin-like growth factor, IGF-1, a byproduct of increased GH levels caused by acromegaly, on injectable somatostatin analogs at baseline (average IGF-1 £ 1.0 x upper limit of normal (ULN)). The patients must also have confirmed active acromegaly following their last surgical intervention based upon an elevated IGF-1 at that time of ³1.3 x ULN. The trial will be randomized on a 1:1 basis to octreotide capsules or placebo. Patients will be dose titrated from 40 mg per day to up to a maximum of 80 mg per day, equaling two capsules in the morning and two capsules in the evening. Patients meeting predefined biochemical failure withdrawal criteria in either treatment arm during the course of the trial will be considered treatment failures and revert to their original treatment of injections and will be monitored for the remainder of the trial. The primary endpoint of the study is the proportion of patients who maintain their biochemical response compared to placebo at the end of the nine-month double-blind, placebo controlled period as measured using the average of the last two IGF-1 levels £ 1.0 x ULN. The hierarchical secondary endpoints that will be considered by the FDA in evaluating the totality of evidence for octreotide capsules treatment effect include:

Proportion of patients who maintain GH response at week 36 compared to screening;

Time to loss of response: IGF-1 > 1.0×ULN;

Time to loss of response: IGF-1 > 1.3×ULN;

Change from screening to end of treatment in mean GH; and

Change in IGF-1 from baseline to end of treatment.

The FDA required that the last two secondary endpoints be analyzed by comparing the octreotide capsules treatment arm to the placebo treatment arm at the end of the nine month, double-blind placebo controlled phase, including those patients that have been rescued by injectable somatostatin analogs. We estimate that as many as 90% or more,

Table of Contents

of the placebo-treated patients may require rescue therapy. As such, we have agreed to analyze the octreotide capsules treatment arm versus the placebo arm at the end of the study. We expect in particular the placebo arm will be highly populated with patients on injectable somatostatin analog rescue therapy. This analysis is referred to in statistical parlance as an ITT estimand. While we do not believe that superiority of Mycapssa will be demonstrated in these last two endpoints, we do believe that if we statistically achieve the primary efficacy endpoint, that is, the proportion of patients who maintain their biochemical response compared to placebo at the end of the nine-month double-blind placebo controlled period, and successfully achieve superiority in the higher-priority secondary endpoints, the totality of evidence supporting a robust treatment effect of octreotide capsules should be clear from the OPTIMAL trial. We anticipate that the FDA will review the totality of the data collected from the CHIASMA OPTIMAL trial, including both primary and secondary endpoints and whether the data collected are sufficiently robust to support the interpretability of these analyses, in determining whether to approve our NDA, if submitted, for the marketing and sale of octreotide capsules. We initiated the CHIASMA OPTIMAL trial in September 2017 and anticipate more than 50 clinical sites will be dedicated to CHIASMA OPTIMAL. We currently expect to release top-line data from this trial by the end of 2019.

CHIASMA OPTIMAL Phase 3 Clinical Trial Design

European Regulatory Pathway

We also intend to seek regulatory approval of octreotide capsules for the treatment of acromegaly in Europe utilizing the hybrid application pathway, which is analogous to the 505(b)(2) regulatory pathway in the United States. In addition to the clinical data we previously submitted to the FDA, the EMA has advised us that a clinical trial demonstrating non-inferiority of octreotide capsules compared to injectable somatostatin analogs as active controls will be required prior to regulatory approval by EMA. Our MPOWERED Phase 3 clinical trial protocol has been accepted by the EMA and we initiated this trial in March 2016.

MPOWERED Phase 3 Clinical Trial

Comparative effectiveness is an important regulatory consideration in Europe. After agreeing to the clinical trial protocol with the EMA, we initiated an international Phase 3 clinical trial of octreotide capsules in acromegaly in March 2016 to show parallel comparative safety and effectiveness.

This trial is called MPOWERED, **M**aintenance of Acromegaly **P**atients with **O**ctreotide Capsules Compared **W**ith Injections - **E**valuation of **Re**sponse **D**urability. This trial is an open-label, randomized, active-controlled study of octreotide capsules in patients who have been classified in the study as responders to a once-a-month injectable somatostatin analog based on criteria comparable to the criteria utilized in our completed Phase 3 clinical trial. This trial is intended to demonstrate non-inferiority, comparing efficacy responses as between two randomized groups of patients who demonstrated response to octreotide capsules. We now believe that approximately 130 patients will be required to enter the 6-month run-in phase of the trial in order to achieve the target 80 octreotide capsules responders randomized to the 9-month comparator phase of the 15-month trial, the number requested by the EMA. In September 2017, we announced that we had surpassed 50% patients randomized in the MPOWERED trial. We currently expect to enroll approximately 130 patients in the trial in the

9

Table of Contents

United States, Europe, Russia and other foreign countries. We currently have 21 sites enrolling patients. Based upon our first Phase 3 trial experience with octreotide capsules, we had estimated approximately 150 patients would be required to enter the run-in phase, but thus far, the aggregate number of patients withdrawing or not responding to octreotide capsules during the run-in phase is lower than originally expected. Each patient will initially receive a daily dose of 40 mg of octreotide capsules, which will be increased up to a maximum of 80 mg daily dose if lower doses are not effective. Similar to the requirements of our first completed Phase 3 clinical trial and the CHIASMA OPTIMAL trial, patients will be required to take octreotide capsules on an empty stomach.

A minimum of 80 patients identified as responders (IGF-1 <1.3 x ULN and GH<2.5 ng/mL) will be randomized (2:3) to either a long-acting injectable somatostatin analog or octreotide capsules at the appropriate dose identified during the run-in phase, and followed for nine months. After completion of this randomized controlled phase, we expect that all eligible patients will have the option of entering an extension phase during which period these patients would receive octreotide capsules at the dose identified during the run-in phase. Patients who do not respond during the run-in phase will not enter the randomized phase but will be switched back to long-acting injectable somatostatin analog and followed for an additional three months.

The primary efficacy endpoint for this trial will relate to IGF-1 with responders defined as patients who achieve an IGF-1 level less than 1.3 times the ULN adjusted for age, the same IGF-1 efficacy criteria utilized in our first, completed Phase 3 clinical trial. Measurements of IGF-1 will be taken throughout the randomized phase of the trial and a time weighted average of these biochemical measures will be calculated. In addition, assessment of symptom control and patient reported outcomes are expected to be included.

In selected centers, patients who are non-responders, but have modestly elevated IGF-1 levels on octreotide capsules alone, may be offered the opportunity to determine if they can respond to a combination of octreotide capsules with a second oral agent called cabergoline. Cabergoline is used for the treatment of mild acromegaly. It has a different mechanism of action and publications have suggested it may have an additive effect to somatostatin analogs. This sub-study, which the EMA did not accept as part of the final protocol for comparative effectiveness, is unlikely to be sufficient to gain regulatory approval for the combination of both drugs but may provide useful information to physicians.

The FDA has advised us in late 2016 that the MPOWERED clinical trial will not be sufficient to address the concerns identified by the FDA in the CRL. Following the FDA s position that the MPOWERED clinical trial will not be sufficient to address the concerns in the CRL, we modified certain elements of the MPOWERED study in an effort to preserve patients, sites and other resources necessary to conduct the Phase 3 CHIASMA OPTIMAL trial addressing the FDA s concerns and produce data packages that could be suitable for submission in both the United States and the European Union. We currently expect to release top-line data from the MPOWERED trial in 2020.

MPOWERED Phase 3 Design to Support EMA Application

Table of Contents

Completed Phase 3 Clinical Trial

In March 2012, we initiated a Phase 3 multi-center, open-label, baseline-controlled clinical trial to evaluate the safety and efficacy of octreotide capsules in patients with acromegaly who responded to and tolerated treatment with somatostatin analogs. We completed this trial in November 2014 and the results were published in the *Journal of Clinical Endocrinology & Metabolism* in February 2015 and presented at the Endocrine Society s Annual Meeting in March 2015. To date, octreotide capsules is the first and only somatostatin analog formulated for oral administration to complete a Phase 3 clinical trial. In addition, the results were submitted with our NDA for octreotide capsules in June 2015, and in the FDA s CRL to our NDA, the FDA expressed concerns regarding certain aspects of the company s single-arm, open-label Phase 3 clinical trial and strongly recommended that we conduct a randomized, double-blind and controlled trial that enrolls patients from the United States and is of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. In the minutes from our End of Review Meeting, the FDA indicated that some of its concerns could potentially be addressed through a placebo-controlled study design, which we have sought to address with CHIASMA OPTIMAL.

Trial Design

A total of 155 patients with acromegaly, each of whom was classified according to the study parameters as a responder to a long-acting injectable somatostatin analog, were enrolled in the trial. Two weeks after their last monthly injection of the long-acting injectable somatostatin analog, patients were reassessed to obtain baseline IGF-1 and GH levels. Both the screening and baseline measurements were performed while patients were still on active injection therapy. The 155 patients enrolled in the trial are referred to as the intent to treat, or ITT, group.

After baseline levels were obtained, no less than one month following their last monthly injection of the long-acting injectable somatostatin analog, a core treatment period with octreotide capsules was initiated. This core treatment period consisted of a dose-escalation phase of at least two months in duration, designed to find an appropriate dose of octreotide capsules for each individual patient, and a fixed-dose phase of up to five months in duration, during which period the appropriate therapeutic dose identified in the dose-escalation phase was maintained. Since data from our prior clinical trials demonstrated a significant reduction in bioavailability when octreotide capsules are administered with a high-fat meal, patients in this Phase 3 clinical trial were required to fast for at least one hour before and at least one to two hours after each dose.

Patients who entered the core treatment phase of the trial initially received a 40 mg daily dose (administered in two pills a day), which was increased to daily doses of 60 mg or 80 mg on an as-required basis to maintain biochemical response and/or symptom control, at the discretion of the investigator. For each patient, the core treatment phase lasted for seven months after his or her first dose of octreotide capsules. Patients could then opt to continue treatment with octreotide capsules during an extension period of up to an additional six months, with a two-week period for final follow-up. Four patients dropped out of the trial after receiving at least one dose of octreotide capsules but before a biochemical response could be measured, resulting in a modified intent to treat, or mITT, group of 151 patients.

The primary objective of the trial was to determine the efficacy of octreotide capsules in patients with acromegaly, as measured by effect on IGF-1 and GH levels, with responders defined as patients who achieve an IGF-1 level less than 1.3 times the upper limit of normal, or ULN, adjusted for age and an integrated GH level over two hours less than 2.5 ng/mL. Secondary objectives included assessment of safety and tolerability of octreotide capsules, and comparison of efficacy of octreotide capsules versus long-acting injectable somatostatin analog.

11

Table of Contents

Completed Phase 3 Clinical Trial Design

Trial Results

Of the 155 patients enrolled, four were not evaluable and of the 151 in the mITT group, 49 patients discontinued, the majority during the dose-escalation phase. Of the 151 patients in the mITT group, patients discontinued for a variety of reasons, including treatment failures because the patient could not be controlled in the study on 80 mg, the highest dose available (24); withdrawals due to adverse events (18); or patient choice, sponsor request and lost to follow up (7). Of the 110 patients that completed the dose-escalation phase, 52 patients, or 47%, were receiving the 40 mg daily dose, 25 patients, or 23%, were receiving the 60 mg dose, and 33 patients, or 30%, were receiving the 80 mg dose.

After completion of the dose-escalation phase, the remaining 110 patients entered the fixed dose phase of the core treatment period and continued on octreotide capsules at their respective doses until seven months after first dosing. A total of 102 patients completed the fixed dose phase of the trial, 88 of whom, or 86%, voluntarily chose to remain on octreotide capsules during the six-month extension phase, for a total of 13 months of treatment after first dosing. A total of 82 patients completed the six-month extension phase of the trial.

Overall, 65% of patients in the mITT group were classified as responders at the end of the seven-month core treatment phase, which was the primary endpoint for the trial. Applying a worst-case imputation method, whereby all patients who withdrew from the study prematurely (regardless of reason) are treated as non-responders, 53% of patients were classified as responders at the end of the seven-month core treatment phase. By the end of the six-month extension phase, or 13 months after first dosing, the responder rate was 62% in the mITT group. Of the 110 patients that completed the dose-escalation phase, and therefore received an optimized dose of octreotide capsules, 75% were classified as responders. For all 151 patients included in the mITT group, the responder rate on long-acting injectable somatostatin analogs was 89% at baseline, prior to initiation of octreotide capsules. Endocrinologists indicated to us that effectiveness in at least 50% of patients treated would be sufficient for an oral treatment to generally be prescribed by physicians.

Table of Contents

Overall Phase 3 Response in mITT Group vs. Baseline

We further assessed the quality of the responses to octreotide capsules in the patients studied. The quality of the patient responses on octreotide capsules was comparable to the quality of the responses on injectable therapies. In the mITT group, mean GH levels for patients on octreotide capsules were below the baseline values on injectable therapies at all time points assessed through the end of the extension phase. The median GH level in the mITT group at baseline was 0.77 ng/mL, which dropped to 0.40 ng/mL within two hours of the first dose of octreotide capsules and 0.49 ng/mL by the end of the extension phase, 13 months later. IGF-1 levels were stably maintained below 1.3 times the ULN for up to 13 months in the mITT group.

GH and IGF-1 Response in mITT Group Throughout the Duration of the Phase 3 Trial

We also assessed control of acromegaly symptoms, the incidence of symptoms, and the severity and number of symptoms in patients using octreotide capsules in a retrospective analysis performed after completion of the trial. At baseline, 81% of patients in the mITT group, the majority of whom were classified as responders, still had acromegaly symptoms, such as headaches, excessive perspiration, muscle weakness and/or joint pain and swelling. Patients who completed 13 months of treatment reported significantly fewer acromegaly symptoms at the conclusion of the trial than at the time of their baseline screening, and this result was statistically significant, with p-values of less than 0.020. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less is generally considered to represent statistical significance, meaning that there is a less than 1-in-20 likelihood that the observed results occurred by chance. There was also a reduction in the severity of symptoms reported. In addition, a questionnaire conducted in a subset of the patients in the clinical trial reported that breakthrough symptoms of acromegaly were experienced by 36% of patients receiving injections at baseline compared to 22% at 13 months on octreotide capsules.

Table of Contents

Reduced Number of Acromegaly Symptoms at Conclusion of Phase 3 Trial

(Fixed Dose Population (n = 110))

The safety profile of octreotide capsules in the trial was consistent with the known safety profile of octreotide and the disease burden of acromegaly, with the most common adverse events observed in the gastrointestinal system, such as nausea and diarrhea, the nervous system, such as headaches, and the musculoskeletal system, such as joint pain, but without adverse injection-site reactions. No new or unexpected safety signals were observed in the study. While the FDA did not note any safety concerns related to octreotide capsules in the CRL, it subsequently indicated in the End of Review meeting minutes that the size, duration, dropout rate and absence of a control group in our Phase 3 clinical trial were factors limiting an overall safety assessment.

We only performed statistical analysis on the symptom reductions for our Phase 3 trial of octreotide capsules in acromegaly and did not perform statistical analysis related to the biochemistry, specifically the reduction in GH and IGF-1 levels.

Phase 1 Clinical Trials of Octreotide Capsules

Together with a group of academic collaborators, we conducted a series of Phase 1 clinical trials to demonstrate that the bioavailability of octreotide capsules, developed utilizing our TPE technology, is comparable to the

Table of Contents

bioavailability of octreotide administered in the short-acting subcutaneous, or sc, formulation. These trials demonstrated similar pharmacokinetics for octreotide capsules and octreotide 0.1 mg sc injection and that a 20 mg oral dose of octreotide capsules produced systemic exposure comparable to octreotide 0.1 mg sc injection in healthy volunteers. There was no effect of route of administration on octreotide elimination, and the mean elimination half-life (t1/2) was comparable with the two treatments. However, these studies also demonstrated that the bioavailability of octreotide capsules are approximately 90% lower when it is taken with a high-fat meal rather than in the fasted state. Accordingly, all of our Phase 3 clinical trials required fasting for at least one hour before and at least one to two hours after each dose.

Pharmacokinetics of Octreotide capsules vs. SC Octreotide in Phase 1 Trial

In addition, to demonstrate the bioactivity of octreotide capsules, as measured by reduction in GH levels, we conducted a Phase 1 clinical trial in 16 healthy volunteers. In this crossover study, a single 20 mg dose of octreotide capsules was shown to suppress mean GH levels below 0.25 ng/mL ($p < 0.05$). This is similar to the effect seen in published results using octreotide injections.

Suppression of GH Levels in Healthy Volunteers

Also in this trial, we evaluated the ability of octreotide capsules to suppress GH levels in healthy subjects whose production of GH had been transiently stimulated by dosing with growth hormone-releasing hormone, or GHRH, and arginine. GHRH and arginine are used in routine clinical testing for deficiencies in GH production. In a

Table of Contents

healthy person, their administration leads to a large increase in GH levels, which is what was observed in this trial. A single 20 mg dose of octreotide capsules lowered the levels of GH by 80% ($p < 0.001$) following dosing with GHRH and arginine.

Data from our Phase 1 bioavailability and bioactivity clinical trials were published in the *Journal of Clinical Endocrinology & Metabolism* in July 2012.

A total of 11 clinical pharmacology studies have evaluated the safety of octreotide capsules. In all of these studies, the safety profile of octreotide capsules was consistent with the known safety profile of the short-acting octreotide 0.1 mg sc injection. No new or unexpected safety issues were detected during any of the clinical pharmacology studies. In particular, no new safety issues related to the novel formulation or route of administration were observed. While the FDA did not note any safety concerns related to octreotide capsules in the CRL, it subsequently indicated in the End of Review meeting minutes that the size, duration, dropout rate and absence of a control group in our Phase 3 clinical trial were factors limiting an overall safety assessment.

Other Potential Indications for Octreotide Capsules

If we receive regulatory approval for octreotide capsules in acromegaly, we may pursue the development of octreotide capsules in other indications. At this time, we do not currently have the personnel or financing to simultaneously pursue the development of octreotide capsules in indications other than acromegaly.

Our Proprietary Transient Permeability Enhancer Technology Platform

Our Transient Permeability Enhancer, or TPE, technology is a proprietary platform, developed internally by our scientists, that enhances the absorption through the intestinal wall of drugs that otherwise would not be absorbed efficiently by that route. Using our TPE technology, we can transiently and reversibly open the so-called tight junctions between the cells lining the inner intestinal wall, enabling drug molecules to be absorbed intact. Our TPE formulation is a suspension of water-soluble particles containing a precise combination of medium-chain fatty acid salts and drug substance in a fat-soluble medium. In creating a TPE formulation, we make no chemical modifications to the drug substance.

Oral delivery of peptides and nucleic acids is limited due to their inherent vulnerability to digestive processes and their poor intestinal absorption. The same intestinal absorption limitation applies to certain small molecules that have poor bioavailability. The cells at the surface of the intestine, columnar epithelial cells, are connected by tight junctions that form a barrier preventing permeation by water-soluble molecules as well as by viruses and bacteria. Our TPE technology induces the transient opening of these tight junctions, allowing peptides and other macromolecules up to a certain size, but not toxins, viruses and bacteria, to cross the intestinal barrier and enabling access to the blood.

The permeability of intestinal tight junctions is known to be altered by a number of dietary factors such as fatty acids, polysaccharides and flavonoids. Transient, reversible opening of the tight junctions and an increase in epithelial permeability are a normal part of intestinal physiology. These permeability adjustments allow the gut to balance two opposing functions: creating a barrier to the passage of microorganisms while facilitating the absorption of nutrients following a meal. In developing the TPE platform, our goal was to establish the ability to reproducibly induce transient increases in the permeability of tight junctions, allowing absorption of specifically formulated drug molecules.

We have conducted extensive nonclinical studies to demonstrate the ability of our TPE technology to increase the permeability of the intestinal epithelial layer and therefore absorb molecules of different shapes, sizes and doses. As a

result of these studies, we believe that our TPE technology can be applied to multiple additional peptide drug products as well as small molecules with poor bioavailability.

Table of Contents

Our TPE Platform

Although not currently staffed or sufficiently financed to do so, if octreotide capsules are approved in acromegaly, we may seek to use our TPE platform to develop other oral medications to help improve the lives of patients suffering from other debilitating diseases that are currently being treated with injectable therapies. If we pursue new peptide-based drugs to develop using our TPE platform, to potentially reduce the development time and expenses and overall level of investment required, where possible, we may focus our efforts on drugs for which we may utilize the FDA s 505(b)(2) regulatory pathway in the United States and the hybrid application pathway, which is analogous to the 505(b)(2) regulatory pathway, in Europe. In March 2017, the Tufts Center for the Study of Drug Development reported that the 505(b)(2) regulatory pathway for new drug applications in the United States has not led to shorter approval times. With octreotide capsules, we brought a TPE-based product candidate from concept to the first clinical trial within 18 months and then initiated a Phase 3 study approximately two years later.

Prior License Agreement with Roche

In January 2013, we entered into a license agreement with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc., collectively Roche, for the development and commercialization of octreotide capsules. Under the terms of the license agreement, we had responsibility for continued clinical development through completion of our initial Phase 3 clinical trial, establishment of commercial-scale manufacturing and completion of ongoing nonclinical activities. Roche assumed responsibility for development and commercialization thereafter. The agreement provided for an upfront payment of $65.0 million, future consideration of up to $530 million in development and commercial milestones, and the right to receive tiered, double-digit royalties on net sales of octreotide capsules.

In January 2014, we received the clinical results from the seven-month core treatment period of the octreotide capsules Phase 3 clinical trial. These results did not include the six-month extension period of the trial, which allowed patients the opportunity to choose to continue on oral therapy. In May 2014, Roche conducted a pre-NDA meeting with the FDA. In July 2014, Roche elected to terminate the license agreement and transitioned octreotide capsules and all materials related to the clinical development programs back to us. We subsequently entered into a termination agreement with Roche, which included our purchase of active pharmaceutical ingredient for future manufacturing of octreotide capsules and a trademark associated with octreotide capsules for an aggregate of $5.1 million payable over three years. We have no further obligations to Roche.

In October 2014, we completed analyses of the full 13-month clinical results from our Phase 3 clinical trial of octreotide capsules. Subsequently, in December 2014, we met with the FDA to discuss our clinical development of octreotide capsules, including the full 13-month data from our Phase 3 clinical trial. Based on the results of this meeting, we submitted an NDA to the FDA in June 2015. In April 2016, the FDA issued a CRL to our NDA.

Table of Contents

Commercialization Strategy

We retain worldwide rights to develop and commercialize octreotide capsules with no royalty obligations to third parties. We may commercialize octreotide capsules, if approved, ourselves in the United States employing a strategy that differentiates our product and is tailored to the needs of patients and their physicians. Prior to the receipt of the CRL, we conducted market research and other pre-commercial activities in the United States to better understand satisfaction levels and key unmet needs with respect to current treatments for acromegaly and to build awareness of octreotide capsules. This market research has been conducted with endocrinologists, nurses and patients with acromegaly. In surveys commissioned by us, more than 80% of patients with acromegaly expressed a preference for an oral treatment, and endocrinologists surveyed predicted that an oral treatment would ultimately become the preferred treatment option. Endocrinologists indicated that effectiveness in at least 50% of patients treated would be sufficient for an oral treatment to generally be prescribed by physicians. To assess the attitudes of commercial third-party payors toward reimbursement for octreotide capsules, in 2010 we conducted research with 12 such payors collectively representing 111 million covered lives. Payors representing nearly 90% of these covered lives said they would reimburse an oral treatment assuming pricing was in a range comparable to the existing injectable therapy market leader, octreotide.

We believe the current U.S. market for acromegaly treatments is concentrated. We believe that approximately 8,000 adult acromegaly patients are chronically treated with somatostatin analogs in the United States, and that approximately 90% of these patients are managed by fewer than 1,000 accounts. Patients with acromegaly undergoing treatment in the United States are treated by endocrinologists at a small number of academic institutions with pituitary experts (pituitary centers), regional academic centers or hospital systems (regional referral centers) and some community endocrinologists. We believe we will be able to market octreotide capsules, if approved, to pituitary centers, regional referral centers and high-volume community endocrinologists. We believe that the clinical benefits, if demonstrated, and preferences of patients and healthcare professionals for an oral therapy together with our planned patient-centric approach could enable octreotide capsules, if approved, to become a new standard of care in acromegaly.

We intend to seek approval to commercialize octreotide capsules in Europe following the completion of our ongoing Phase 3 MPOWERED trial, and, if successful, plan to submit an MAA to the EMA. We plan to explore the strategic merits of collaboration opportunities for commercializing octreotide capsules in Europe and the rest of the world in order to maximize the availability of the product candidate, if approved, to patients. However, depending on our evaluation of the strategic merits of these collaboration opportunities, we may decide to retain commercial rights in key markets.

Manufacturing

We depend on third-party suppliers and contract manufacturing organizations, or CMOs, for all of our required raw materials and drug substance and to manufacture and package drug product for clinical use and commercial use, if approved. If octreotide capsules are approved, we plan to establish a distribution channel in the United States utilizing third-party logistics and specialty pharmacies to distribute product directly to patients who have been prescribed octreotide capsules.

We have qualified Novetide Ltd., a subsidiary of Teva API Pharmaceuticals Industries (TAPI) Ltd., in Israel, and Bachem Americas Inc., in the United States, as suppliers of the generic active pharmaceutical ingredient, or API, octreotide acetate.

All excipients, or substances formulated together with the API, used in manufacture of octreotide capsules are readily available. The octreotide API is formulated with our TPE technology by Lyophilization Services of New England Inc. and filled into capsules and enteric-coated by Capsugel, a division of Lonza, in Scotland. All manufacturers periodically undergo inspections by regulatory authorities.

Octreotide capsules are refrigerated and our NDA included primary stability data covering 24 months under these storage conditions. We have since demonstrated 36 months refrigerated stability for octreotide capsules and plan

Table of Contents

to update our NDA accordingly upon resubmission. We have also obtained data regarding additional one-month storage at room temperature to support storage of octreotide capsules at room temperature. The FDA has previously indicated that the testing parameters for our control strategy and product release and stability specifications are acceptable. The manufacturing process for the API has been validated at both of our API manufacturers and octreotide capsules manufactured at our CMOs as well as final product packaging has also been validated. In the CRL, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval of our NDA. In December 2016, we were informed that the supplier had recently received its EIR from the FDA. The receipt of the EIR is an indication that the FDA has concluded its inspection of the supplier and as of the date of its report considers outstanding deficiencies resolved. We expect that our suppliers will be subject to additional regulatory inspections in the future, including in connection with the FDA s review of any NDA we may submit in the future, if any, seeking approval of octreotide capsules in acromegaly.

Competition

Our industry is highly competitive and subject to rapid and significant technological change as researchers learn more about diseases and develop new technologies and treatments. Our potential competitors include primarily large pharmaceutical, biotechnology companies and specialty pharmaceutical companies. Key competitive factors affecting the commercial success of octreotide capsules and any other product candidates we may develop are likely to be efficacy, safety and tolerability profile, reliability, convenience of administration, price and reimbursement and effectiveness of our promotional activities.

The standards of care for patients suffering from acromegaly all involve injectable therapies, other than cabergoline, an oral agent used for the treatment of mild acromegaly. Novartis markets octreotide LAR, which is administered monthly and intramuscularly using a large gauge needle. Ipsen markets lanreotide, another long-acting analog of somatostatin, like octreotide, which is administered monthly using a deep subcutaneous injection. Both therapies, which are most frequently the first drug treatment options for patients, involve side effects related to the injections and inconvenience due to the timing and requirements of the injections. Pfizer markets pegvisomant daily injections and Novartis also markets pasireotide LAR, which is another somatostatin analog administered via intramuscular injection. Pegvisomant daily injections and pasireotide LAR are significantly more costly than injectable octreotide and lanreotide. The label for pasireotide LAR includes a warning about hyperglycemia and diabetes, which can sometimes be severe. The label advises healthcare professionals administering pasireotide LAR to monitor glucose levels periodically during therapy and to monitor glucose levels more frequently in the months that follow initiation or discontinuation of therapy and following dose adjustment. We are aware of other companies involved in early-stage nonclinical and clinical studies of similar somatostatin analogs, but most involve administration via injection. Most notably, Camurus AB., in partnership with Novartis, is developing CAM2029, a subcutaneous octreotide depot for the potential treatment of neuroendocrine tumors and acromegaly. Published reports indicate that Camurus AB intends to communicate updated project time-lines for the start of their Phase 3 program in mid-2018 which may directly compete with us for the limited number of acromegaly patients willing to participate in our current clinical trials. MidaTech Pharma PLC also recently announced plans to conduct its first in human study of Q-Octreotide (MTD201), Midatech s injectable treatment for acromegaly built on its Q-Sphera sustained release platform technology. Assuming positive clinical data, Midatech anticipates a launch as early as 2020. In October 2017, Crinetics Pharmaceuticals, Inc. announced the initiation of a Phase 1, double-blind, randomized, placebo-controlled, single- and-multiple-dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of CRN00808 in healthy volunteers. CRN00808 is a nonpeptide somatostatin agonist designed to be taken orally. In May 2017, Dauntless Pharmaceuticals, Inc., a privately held biopharmaceutical company announced positive results from its two-part, Phase 1 pharmacokinetic/pharmacodynamic study evaluating DP1038, a novel formulation of octreotide acetate for intranasal administration. If any or a combination of CAM2029, MTD201, CRN00808 or DP1038 and our octreotide capsules

receive regulatory approval in a similar timeframe, we may face difficulties with our commercial launch with one or more new competitive products launching simultaneously or in similar timeframes.

Table of Contents

Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval of drugs and achieving widespread market acceptance. Our competitors drugs, or drugs they may develop in the future, may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render octreotide capsules or any future product candidates we may develop obsolete or non-competitive before we can recover the expenses of developing and commercializing octreotide capsules or any future product candidates we may develop. Our competitors may also obtain FDA or other regulatory approval of their products more rapidly than we may obtain approval of ours, especially in light of the expected timing of our release of top-line data from the CHIASMA OPTIMAL trial by the end of 2019. We anticipate that we will face intense and increasing competition as new drugs enter the market and more advanced technologies become available. If we are unable to compete effectively, our opportunity to generate revenue from the sale of octreotide capsules or any future product candidates we may develop, if approved, will be adversely affected.

Intellectual Property

We strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents intended to cover our product candidates and compositions, their methods of use and processes for their manufacture, and any other aspects of inventions that are commercially important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of treatment, and dosage regimens identified in the course of our business. Our success will depend on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position. We seek to obtain domestic and international patent protection, and endeavor to promptly file patent applications for new commercially valuable inventions.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings or derivation proceedings declared by the U.S. Patent and Trademark Office, or the USPTO, to determine priority of invention.

Patents

As of March 1, 2018, our patent portfolio includes four patents issued in the United States; patents issued in foreign jurisdictions; patent applications pending in the United States; and patent applications pending in various

Table of Contents

foreign jurisdictions. These patents and patent applications include narrow and broad claims directed to polypeptide compositions including octreotide compositions formulated with our TPE technology; capsules containing such compositions; methods of treatment using such compositions; and methods of making various compositions with our TPE technology. This patent family includes three issued U.S. patents and one pending patent application with claims directed to enteric-coated oral dosage form comprising octreotide compositions, capsules containing octreotide compositions, and methods of treating various conditions with related octreotide compositions. Other patents in this family have issued in Australia, Canada, China, Europe, Hong Kong, Israel, Japan, Korea, Mexico, New Zealand, Russia, South Africa, and the United Kingdom, and patent applications are pending in other jurisdictions, including Brazil, Canada, China, Europe, Israel and Korea, Mexico, Russia, Australia, and Japan. Patents in this family are expected to expire in 2029, absent any adjustments or extensions. This patent family also includes a 4th issued U.S. patent with claims relating to enteric-coated oral dosage form comprising polypeptide compositions.

We also own two Patent Cooperation Treaty, or PCT, patent applications with claims directed to further uses of octreotide. Patents issuing from any United States nonprovisional and foreign-filed patent applications claiming priority to these PCT applications are expected to expire in 2035 for one PCT application and 2037 for the other PCT application, absent any adjustments or extensions.

We also own a PCT patent application directed to a dosage regimen for octreotide and also directed to methods of treating acromegaly with certain octreotide-containing compositions and dosage regimens. There are corresponding pending applications in the United States and abroad. Patents issuing from any U.S. nonprovisional and foreign-filed applications claiming priority to this PCT application are expected to expire in 2036, absent any adjustments or extensions.

Additionally, we own two US utility patents directed to proprietary packaging for distribution of octreotide capsules which are expected to expire in 2035, absent any adjustments or extensions. We also own two U.S. design patents, which have been granted in several other jurisdictions and are expected to expire in the U.S. in 2030 and 2033.

Finally, we own one pending PCT patent application directed to further uses of our TPE technology.

Patent Term

The base term of a U.S. utility patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority. The base term of a U.S. design patent is 14 years from issuance for designs filed before the Patent Law Treaties Implementation Act of 2012 which took effect on May 13, 2015 and 15 years from issuance for designs filed after May 13, 2015. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the USPTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products such as our product candidate, octreotide capsules. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

21

Table of Contents

United States Drug Development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require 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 to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA s refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, voluntary product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Octreotide capsules must be approved by the FDA through the NDA process before it may be legally marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of extensive nonclinical, or preclinical, laboratory tests, animal studies and formulation studies in accordance with applicable regulations, including the FDA s Good Laboratory Practice, or GLP, regulations;

- submission to the FDA of an IND, which must become effective before human clinical trials may begin;

- performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical study related regulations, sometimes referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for its proposed indication;

- submission to the FDA of an NDA;

- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with the FDA s current good manufacturing practice requirements, or cGMP, to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity;

- potential FDA audit of the clinical trial sites that generated the data in support of the NDA; and

- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

The data required to support an NDA are generated in two distinct development stages: nonclinical and clinical. For new chemical entities, the nonclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the nonclinical tests must comply with federal regulations and requirements including GLPs. The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or published literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human studies. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any

time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers and/or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor s control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completion. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

Clinical trials are generally conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3 clinical trials, and may overlap. Phase 1 generally involves a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these studies is to assess the metabolism, pharmacological action, side effect tolerability and safety of the drug. Phase 2 trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks and preliminary evaluation of efficacy. Phase 3 trials generally involve large numbers of patients at multiple sites, and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product approval. Phase 3 trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, FDA may mandate the performance of Phase 4 trials.

Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events, findings from other studies or animal or *in vitro* testing that suggest a significant risk to humans exposed to the drug and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution 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. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring

board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the study. The clinical trial sponsor may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate.

Table of Contents

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA Review Process

Following trial completion, trial data are analyzed to assess safety and efficacy. The results of nonclinical studies and clinical trials are then submitted to the FDA in an NDA along with proposed labeling for the product and information about the manufacturing process and facilities that will be used to ensure product quality, results of analytical testing conducted on the chemistry of the drug, and other relevant information. The NDA is a request for approval to market the drug and must contain proof of safety, purity, potency and efficacy, which is demonstrated by extensive nonclinical and clinical testing. The application includes both negative or ambiguous results of nonclinical studies and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product to the satisfaction of the FDA. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. FDA approval of an NDA must be obtained before marketing a drug in the United States.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug 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. The FDA may grant deferrals for submission of data or full or partial waivers. An NDA applicant must submit to the FDA a pediatric study plan typically 60 days after an end-of-Phase 2 meeting with the FDA. Because octreotide capsules received orphan drug designation for the treatment of acromegaly, we do not need to comply with the requirements of PREA at this time. If, however, we seek other indications for octreotide capsules or pursue approval of any other product candidate that does not have orphan drug designation, we may need to comply with PREA or otherwise seek a waiver.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. The decision to accept the NDA for filing means that the FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has ten months from the receipt of an NDA for a non-new molecular entity in which to complete its initial review of a standard NDA and respond to the applicant. The FDA does not always meet its PDUFA goal dates for standard NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMPs to assure and preserve the product s identity, strength, quality and purity. The FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and 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 will likely re-analyze the clinical trial data,

which could result in extensive discussions between the FDA and us during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product 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. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form.

A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application or request a hearing. Even if such data and information are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive, and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States, and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a risk evaluation and mitigation strategy, or REMS, to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS; the FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

505(b)(2) Approval Process

Section 505(b)(2) of the FDCA provides an alternate regulatory pathway for the FDA to approve a new drug and permits reliance for such approval on published literature or an FDA finding of safety and effectiveness for a previously approved drug product. Specifically, section 505(b)(2) permits the filing of an NDA where one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The applicant may rely upon published literature and/or the FDA s

findings of safety and effectiveness for a previously approved drug. Typically, 505(b)(2) applicants must perform additional trials to support the change from the previously approved drug and to further demonstrate the new drug s safety and effectiveness. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the section 505(b)(2) applicant.

Table of Contents

Our product candidate, octreotide capsules, is based upon an already approved version of the same drug in an immediate-release formulation for subcutaneous injection, rather than a new chemical entity product candidate. Accordingly, we expect to be able to rely on information from previously conducted studies involving the immediate-release subcutaneous octreotide product in our clinical development plans and our NDA resubmission, if resubmitted.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical company and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse events with the product, providing the regulatory authorities with updated safety and efficacy information, and product sampling and distribution requirements in accordance with the Prescription Drug Marketing Act, a part of the FDCA. Modifications or enhancements to the product or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion and advertising, including direct-to-consumer advertising. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. In addition, a pharmaceutical company must comply with restrictions on promoting drugs for uses or in patient populations that are not described in the drug s approved labeling (known as off-label use), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMPs. We rely on third parties for the production of clinical quantities of octreotide capsules and expect to rely on third parties for the production of commercial quantities of our octreotide capsules, in both cases in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMPs, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market.

The FDA also may require post-marketing testing, known as Phase 4 testing, REMS and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement,

untitled or warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness

Table of Contents

data may require changes to a product s approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA s policies may change, which could delay or prevent regulatory approval of our products under development and impact approved products already on the market.

Other Regulatory Matters

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The failure to comply with regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, voluntary recall, seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, exclusion from federal healthcare programs, or refusal to allow a firm to enter into supply contracts, including government contracts. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or effectiveness of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the voluntary recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

Orphan Designation and Exclusivity

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States. Alternatively, orphan drug designation may be available if the disease or the condition affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. In addition, if a product is the first to receive FDA approval of the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

U.S. Marketing Exclusivity

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDA provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received

approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies

Table of Contents

and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, adds six months of exclusivity, which runs from the end of other exclusivity protection and patent term, and may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued Written Request for such a trial.

Other Regulations

We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection and fire hazard control. We may incur significant costs to comply with such laws and regulations now or in the future.

European Orphan Designation and Exclusivity

In the European Union, the European Commission, after reviewing the opinion of the EMA s Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect not more than five in 10,000 persons in the European Union Community, or when, without incentives, it is unlikely that sales of such products in the European Union would be sufficient to justify the necessary investment in developing the products. Additionally, orphan drug designation is only available where no satisfactory method of diagnosis, prevention, or treatment of the condition has been authorized (or the product would be a significant benefit to those affected).

In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Market exclusivity would not prevent the approval of a similar drug that is shown to be safer, more effective or otherwise clinically superior.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Coverage and Reimbursement

Sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and adequate reimbursement from third-party payors, including government healthcare program administrative authorities, managed care organizations, private health insurers, and other entities. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Therefore, our products, if approved, may not obtain market acceptance unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

The process for determining whether a third-party payor will provide coverage for a drug product typically is separate from the process for setting the price of a drug product or for establishing the reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a

particular indication. A decision by a third-party payor not to cover our product

Table of Contents

candidates could reduce physician utilization of our products once approved. Moreover, a third-party payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved or that any required patient cost-sharing amount will be acceptable to the patient. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. Additionally, coverage and reimbursement for drug products can differ significantly from payor to payor and among the insured lives of an individual payor depending upon the benefits applicable to the insured person. One third-party payor s decision to cover a particular drug product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for drug products and medical services, examining the medical necessity and reviewing the cost effectiveness of drug products and medical services, in addition to questioning safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after FDA approval or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health develop research plans and periodically report on the status of the research and related expenditures to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for governmental or private payors, it is not clear what effect, if any, the research will have on the sales of our product candidates, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates, if and once approved.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved. Historically, products launched in the European Union do not follow price structures of the United States and generally tend to be significantly lower.

Anti-Kickback and False Claims Laws and Other Regulatory Matters

In the United States, among other things, the research, manufacturing, distribution, sale and promotion of drug products are potentially subject to regulation and enforcement by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the United States Department of Health and Human Services (e.g., the Office of Inspector General), the Drug Enforcement Administration, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency, state attorneys general and other state and local government agencies. Our current and future business activities, including for example, sales, marketing and scientific/educational grant programs must comply with healthcare regulatory laws, including the Federal Anti-Kickback Statute, the

Federal False Claims Act, as amended, the privacy regulations

Table of Contents

promulgated under the Health Insurance Portability and Accountability Act, or HIPAA, as amended, physician payment transparency laws, and similar state laws. Pricing and rebate programs must comply with the Medicaid Drug Rebate Program requirements of the Omnibus Budget Reconciliation Act of 1990, as amended, and the Veterans Health Care Act of 1992, as amended. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. All of these activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The Federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of, any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as Medicare or Medicaid. The term remuneration has been broadly interpreted to include anything of value. The Federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Additionally, the intent standard under the Federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the Federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the Federal False Claims Act. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, many states have adopted laws similar to the Federal Anti-Kickback Statute. Some of these state prohibitions apply to the referral of patients for healthcare services reimbursed by any insurer, not just federal healthcare programs such as Medicare and Medicaid. Due to the breadth of these federal and state anti-kickback laws, and the potential for additional legal or regulatory change in this area, it is possible that our future business activities, including our sales and marketing practices and/or our future relationships with endocrinologists and other healthcare providers might be challenged under anti-kickback laws, which could harm us.

The Federal False Claims Act prohibits anyone from, among other things, knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent. This statute has been interpreted to prohibit presenting claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to cause the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. For example, pharmaceutical companies have been found liable under

the Federal False Claims Act in connection with their off-label promotion of drugs. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $11,181 and $22,363 for each separate

Table of Contents

false claim, the potential for exclusion from participation in federal healthcare programs, and, although the Federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the Federal False Claims Act and certain states have enacted laws modeled after the Federal False Claims Act.

Similarly, the civil monetary penalties statute imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

Additionally, HIPAA created federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

The ACA included a provision commonly referred to as the Sunshine Act, which requires certain pharmaceutical manufacturers to track and report annually certain financial arrangements with physicians and teaching hospitals, including any transfer of value provided, as well as any ownership or investment interests held by physicians and their immediate family members. Covered manufacturers are required to submit reports to CMS by the 90th day of each subsequent calendar year. The information reported is publicly available and searchable on the CMS website. There are also an increasing number of state and foreign laws that require manufacturers to make reports to states or foreign governments on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state, federal or foreign authorities. These laws may affect our sales, marketing and other promotional activities by imposing administrative and compliance burdens on us. We are engaging in significant efforts to establish systems and processes in order to comply with these laws and regulations. Failure to comply with the reporting requirements would result in significant civil monetary penalties.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes certain of HIPAA s privacy and security standards directly applicable to business associates, defined as an entity that performs certain functions that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys fees and costs associated with pursuing federal civil actions.

In addition to HIPAA and HITECH, other federal and state laws, including state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use and disclosure of personal information. Many state laws that govern the privacy and security of health information in certain circumstances differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Various foreign countries also have, or are developing, laws governing the collection, use and transmission of personal information. The legislative and regulatory landscape for privacy and data protection

continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business.

Table of Contents

The failure to comply with applicable regulatory requirements subjects us to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in significant criminal, civil and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in federal healthcare programs, such as Medicare and Medicaid, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, refusal to allow us to enter into supply contracts, including government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Even if we are not determined to have violated applicable regulatory or legal requirements, government investigations into alleged violations typically requires the expenditure of significant resources and could generate negative publicity, which could harm our business.

Affordable Care Act and Other Reform Initiatives

In the United States and some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system directed at broadening the availability of healthcare and containing or lowering the cost of healthcare.

In March 2010, the ACA, was enacted. The ACA includes measures that have significantly changed, and are expected to continue to significantly change, the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical industry are the following:

The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services in exchange for state Medicaid coverage of most of the manufacturer s drugs. ACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic products to 23.1% of average manufacturer price, or AMP, and adding a new rebate calculation for line extensions (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP.

The ACA expanded the types of entities eligible to receive discounted 340B pricing, although, with the exception of children s hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs used in orphan indications. In addition, because 340B pricing is determined based on AMP and Medicaid drug rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discounts to increase. The ACA imposed a requirement on manufacturers of branded drugs and biologic agents to provide a 50% (70% commencing January 1, 2019) discount off the negotiated price of branded drugs dispensed to Medicare Part D beneficiaries in the coverage gap (i.e., donut hole).

The ACA imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.

The ACA included the Sunshine Act, which required certain pharmaceutical manufacturers to track and annually report to CMS certain financial arrangements with physicians and teaching hospitals, including any transfer of value provided, as well as any ownership or investment interests held by physicians and their immediate family members.

The ACA established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such

Table of Contents

research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.

The ACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation through 2019.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the individual mandate. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called Cadillac tax on certain high cost employer-sponsored insurance plan, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to reduce the coverage gap in most Medicare drug plans, commonly referred to as the donut hole. Congress may consider other legislation to modify, repeal, or replace elements of the ACA. Thus, the full impact of the ACA, or any law replacing elements of it, on our business remains unclear.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional congressional action is taken. In January 2013, former President Barack Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

European Union Drug Development

In the European Union, octreotide capsules and any future product candidates we may develop will also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if marketing authorizations from the competent regulatory agencies have been obtained.

Table of Contents

Similar to the United States, the various phases of nonclinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the EU countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

On April 16, 2014, the European Commission adopted new clinical trials legislation in an effort to ensure that the rules for conducting clinical trials in the EU will be identical. The new legislation, among other things, will implement a streamlined application procedure with a single entry point for review, harmonize the process for assessing applications for clinical trials, simplify reporting procedures, and increase transparency regarding clinical trials and their outcomes. The legislation, however, is not expected to apply until 2019, at the earliest. Until then, the current law, Clinical Trials Directive 2001/20/EC, continues to govern all clinical trials performed in the EU.

European Union Drug Review and Approval

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

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

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e. in the RMS and the Member States Concerned).

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

concerning its quality, safety and efficacy.

Table of Contents

The approval process and requirements governing the conduct of clinical trials, drug review and approval, product licensing, pricing and reimbursement vary greatly from place to place, and the time in the EEA and other foreign territories may be longer or shorter than that required for FDA approval.

Employees

As of March 1, 2018, we had 16 full-time employees located in the United States and in Israel. While none of our employees are represented by a labor union or party to any collective bargaining agreement, certain provisions of the collective bargaining agreements between the Histadrut (General Federation of Labor in Israel) and the Coordination Bureau of Economic Organizations (including the Industrialists Associations) are applicable to our employees in Israel by extension orders issued by the Israel Ministry of Economy (previously the Israeli Ministry of Trade, Industry and Labor).

Israeli labor laws principally govern the length of the workday, minimum wages for employees, procedures for hiring and dismissing employees, determination of severance pay, annual leave, sick days, advance notice of termination of employment, equal opportunity and anti-discrimination laws and other conditions of employment. Subject to certain exceptions, Israeli law generally requires severance pay upon the retirement, death or dismissal of an employee, and requires us and our employees to make payments to the National Insurance Institute, which is similar to the U.S. Social Security Administration. Our Israeli employees have defined-benefit pension plans that comply with applicable Israeli legal requirements, which also include the mandatory pension payments required by applicable law and allocations for severance pay.

Although we experienced two separate reductions in force in 2016 aggregating greater than 60% of our workforce following our receipt of the CRL, we have never experienced any employment-related work stoppages and believe our relationship with our remaining employees is good.

Research and Development

During the year ended December 31, 2017, our total research and development expense was $17.9 million compared to $31.3 million and $19.0 million in the years ended December 31, 2016 and 2015, respectively. The decrease in 2017 was primarily due to approximately $7.4 million of API purchases and pre-commercial manufacturing validation activities during 2016, that did not reoccur in 2017, as well as reduced compensation-related costs and other research and development program efforts following the reductions of force in June and August 2016. These decreases were partially offset by an increase in clinical trial costs of $1.3 million. The increase in 2016 as compared to 2015 was primarily due to approximately $7.4 million of API purchases during 2016, our ongoing Phase 3 clinical trial of octreotide capsules for the treatment of acromegaly to support the submission of a MAA to the EMA, activities associated with the manufacturing process validation, and an increase in compensation-related expenses due to the hiring of research and development employees.

Corporate Information

We were incorporated under the laws of the State of Delaware and commenced business operations in 2001. Our principal executive offices are located at 460 Totten Pond Road, Suite 530, Waltham, MA 02451 and our telephone number is (617)-928-5300. Our website address is www.chiasmapharma.com. Through our website, we make available, free of charge, our annual report on Form 10-K, quarterly reports on Form 10-Q, proxy statement, current reports on Form 8-K, and any amendments to these reports, as soon as reasonably practicable after we electronically file such material or furnish them to the Securities and Exchange Commission, or the SEC. In addition, the public may read and copy any materials filed by us with the SEC at the SEC s Reference Room, which is located at 100 F Street

NE, Washington, D.C., 20549. Interested parties may call (800) SEC-0330 for further information on the Reference Room. The SEC also maintains a website containing reports, proxy materials and information statements, among other information, at *http://www.sec.gov*. The information contained on our website, or that can be accessed through our website, is not a part of this annual report on Form 10-K and is not incorporated by reference into this Form 10-K.

Table of Contents

We own various U.S. federal and foreign trademark registrations and applications, as well as pending and unregistered trademarks and service marks, including CHIASMA , TPE , MYCAPSSA , MYCAPSSA logo , ACROMEGALY CARE logo and our corporate logo. CHIASMA , MYCAPSSA and TPE are registered U.S. federal trademarks. All trademarks or trade names referred to in this Form 10-K are the property of their respective owners. Solely for convenience, the trademarks and trade names in this Form 10-K may be referred to without the ® and symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display other companies trademarks and trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

Table of Contents

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Annual Report on Form 10-K and in our other public filings before making an investment decision. Our business, prospects, financial condition, or operating results could be harmed by any of these risks, as well as other risks not currently known to us or that we currently consider immaterial. If any such risks or uncertainties actually occur, our business, financial condition or operating results could differ materially from the plans, projections and other forward-looking statements included in the section titled Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere in this report and in our other public filings. The trading price of our common stock could decline due to any of these risks, and as a result, you may lose all or part of your investment.

Risks Related to the Development and Potential Regulatory Approval and Commercialization of Octreotide Capsules and any Future Product Candidates

In light of our receipt of a Complete Response Letter, or CRL, from the FDA in April 2016 regarding our New Drug Application, or NDA, for octreotide capsules for the maintenance treatment of U.S. adult patients with acromegaly, our participation in an End of Review Meeting and several additional interactions with the FDA, and despite our receipt of a Special Protocol Assessment, or SPA for our CHIASMA OPTIMAL Phase 3 clinical trial, the approvability of octreotide capsules is uncertain and we may never obtain regulatory approval in the United States.

In June 2015, we submitted an NDA to the FDA for the marketing and sale of octreotide capsules for the maintenance therapy of adult patients with acromegaly. The NDA was accepted for filing by the FDA in August 2015. On the Prescription Drug User Fee Act, or PDUFA, date of April 15, 2016, the FDA issued a CRL regarding the NDA, indicating that their review was complete and the NDA was not ready for approval in its present form. In its CRL, the FDA advised us that it did not believe our application provided substantial evidence of efficacy to warrant approval, and advised us that we would need to conduct another clinical trial in order to overcome this deficiency. The FDA expressed concerns regarding certain aspects of our single-arm, open-label Phase 3 clinical trial and strongly recommended that we conduct a randomized, double-blind and controlled trial that enrolls patients from the United States and is of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment. In addition, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval. In addition, while the FDA did not note any safety concerns related to octreotide capsules in the CRL, it subsequently indicated in the minutes from our June 2016 End of Review meeting that the size, duration, dropout rate and absence of a control group in our Phase 3 clinical trial were factors limiting an overall safety assessment.

In the End of Review meeting we discussed the concerns raised by the FDA in the CRL, and in the meeting minutes, the FDA reiterated its strong recommendation for a randomized, double-blind and controlled trial, and introduced the concept of a placebo control as a design element that could address some of the FDA s concerns. In August 2017, we reached agreement with the FDA under its SPA procedures of a new Phase 3 clinical trial of octreotide capsules in adult acromegaly patients, which includes a placebo control, which trial, if successful, could potentially enable us to resubmit the NDA. We refer to this new Phase 3 trial, which we initiated in September 2017, using the acronym CHIASMA OPTIMAL. We currently estimate that we will report top-line data from this Phase 3 clinical trial by the end of 2019 and that the NDA, if resubmitted, will qualify for a 6-month review period, but the duration of the trial and time provided for the NDA review, if submitted, could take longer. Although we currently estimate that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations through the anticipated release of top-line data from our Phase 3 CHIASMA OPTIMAL trial by the end of 2019 while supporting our Phase 3 MPOWERED trial in parallel, clinical development is inherently uncertain and therefore we may not have

the sufficient capital resources necessary to achieve this plan. Further, we may not have sufficient capital resources to fully fund this new trial, or any additional trials that the FDA may require as a condition to approval. We also cannot provide any assurance that if we conduct this new Phase 3 clinical trial we will receive U.S. regulatory approval of octreotide capsules for acromegaly.

Table of Contents

Varying interpretations of the data obtained from nonclinical and clinical testing or manufacturing of our product candidates could delay, limit or prevent regulatory approval of octreotide capsules or other product candidates we may develop in the future. Of note, in July 2014, F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc., collectively Roche, elected to terminate our license agreement for octreotide capsules after reviewing the data from the seven-month core treatment period of our first Phase 3 clinical trial of octreotide capsules and after a May 2014 pre-NDA meeting with the FDA. Roche cited no reason for its decision in its formal notice of termination, but stated publicly at the time that it had elected to make this decision after receiving additional information about our first Phase 3 clinical trial and after further consultation with regulatory authorities. Subsequent to this decision, we independently met with the FDA to discuss the clinical development of octreotide capsules, including the first Phase 3 clinical results from the six-month extension phase of the clinical trial (in addition to the seven-month core data provided by Roche in May 2014). At this meeting, the FDA advised us that it had not identified an issue that would preclude us from submitting an NDA for review. However, the FDA also advised us that interpreting efficacy from a voluntary long-term extension study is subject to limitations and therefore the data at the seven-month time point in our first Phase 3 clinical trial would carry more weight in the efficacy evaluation than the extension data. The FDA also informed us that, in its view, a single-arm study was not as informative as a controlled study such as an active control trial using a non-inferiority design, and that the interpretability of the efficacy findings we submitted in our NDA from our single-arm study, and whether these findings would be robust enough to warrant approval, would be review issues as the FDA evaluated our NDA.

If our efforts to address the concerns raised by the FDA in the CRL are unsuccessful in our new Phase 3 CHIASMA OPTIMAL clinical trial or if we fail to meet the primary or secondary endpoints in the trial, we may be unable to obtain U.S. regulatory approval for the marketing and sale of octreotide capsules at all or without submitting new or additional clinical data to the FDA, which may require that we conduct one or more additional clinical trials, which we are highly unlikely to pursue.

Even though our Phase 3 CHIASMA OPTIMAL trial is being conducted under a SPA agreed to with the FDA, we cannot guarantee that the design of, or data collected from, this trial or any of our clinical trials will be sufficient to support filing or approval of an NDA.

In the context of a Phase 3 clinical trial, the purpose of a SPA is to reach agreement with the FDA on the protocol design and size of the trial that may form the primary basis of an efficacy claim in support of an NDA. In requesting a SPA agreement, a sponsor asks focused questions on specific issues relating to the protocol, protocol design, study conduct, study goals and data analysis. However, according to draft regulatory guidance, a SPA agreement does not indicate FDA concurrence on every protocol detail. Absence of an FDA comment on a particular aspect of a trial does not necessarily indicate agreement if the sponsor did not specifically ask about that aspect. Moreover, a SPA is not a guarantee of approval, even if the trial is successful. A SPA is not binding on the FDA and may be rescinded if, for example, the FDA identifies a safety concern related to the product or its pharmacological class, if the FDA and the scientific community recognize a paradigm shift in disease diagnosis or management, if the relevant data, assumptions or information provided by the sponsor in the SPA submission are found to be false or misstated or omit relevant facts, or if the sponsor fails to follow the protocol that was agreed upon with the FDA. A SPA may be modified with the written agreement of the FDA and the trial sponsor and, according to draft regulatory guidance, minor issues can be resolved through additional correspondence and protocol amendments after the trial begins. However, the FDA retains significant latitude and discretion in interpreting the terms of a SPA agreement, the significance of protocol amendments, if necessary after the trial begins, and the data and results from the applicable clinical trial.

Further, the results from the CHIASMA OPTIMAL trial, a double-blind, placebo controlled clinical trial, may not be sufficiently robust to support the filing or approval of an NDA. In particular, the CHIASMA OPTIMAL trial is also expected to have a relatively small sample size, 50 patients enrolled, and therefore the FDA has indicated that missing

data, which might be only a few measurements, may raise questions about data quality and may, ultimately, invalidate the trial results. It should also be noted that the design of the CHIASMA OPTIMAL trial is different in important ways from the design of both our current MPOWERED clinical trial and our completed Phase 3 clinical trial. For example, in contrast to our completed Phase 3 clinical trial, which did not

Table of Contents

have a placebo arm, the CHIASMA OPTIMAL trial design calls for the randomization of 50% of study patients to placebo capsules, the effect of which we cannot predict. We believe conducting a randomized, double-blind and controlled trial, with a placebo control may be particularly challenging. For example, it may be difficult to identify patients with acromegaly willing to enroll in a trial with this design. In our completed Phase 3 clinical trial we used IGF-1 < 1.3 times the upper limit of normal as a screening eligibility criteria and the threshold for response whereas in our CHIASMA OPTIMAL trial we use IGF-1 £ 1.0 times the upper limit of normal. In light of these new trial design elements, even if we achieve a clinical response consistent with or similar to what we believe we achieved in our completed Phase 3 clinical trial, we may fail to achieve the primary or secondary endpoints of the CHIASMA OPTIMAL trial.

We anticipate that both primary and secondary endpoints in the CHIASMA OPTIMAL trial will be taken into account by the FDA in evaluating the totality of evidence for octreotide capsules treatment effect, and mere achievement of the primary endpoint alone may not be sufficient to support approval. Not all endpoints measured may be supportive of octreotide capsules efficacy or safety, particularly those secondary endpoints which measure the biochemical response at the end of the trial of patients taking octreotide capsules as compared to patients rescued by injectable somatostatin analogs. The CHIASMA OPTIMAL trial, as agreed to under SPA, contains secondary endpoints requiring a true intent to treat analysis, or what the FDA refers to as an estimand, that will allow the FDA to compare the difference between treatment arms for all randomized patients at the end of the nine-month, double-blind controlled period, regardless of therapy. As such, the statistical analysis plan requires a biochemical comparison (secondary endpoints measuring both growth hormone and IGF-1) of the patients randomized to octreotide capsules versus patients randomized to placebo at the end of the nine-month, double-blind placebo controlled period, even if those patients require injectable somatostatin analog rescue therapy during the trial. We believe that as many as 90% or more of the patients randomized to placebo could require injectable somatostatin analog rescue therapy during the trial and that octreotide capsules are not likely to demonstrate superiority over injectable somatostatin analogs when evaluated using these secondary endpoint analyses, even if we achieve a statistically significant result of octreotide capsules versus placebo as assessed by the primary endpoint of the trial. Our trial design includes as exploratory endpoints the last observed biochemical values (measuring both growth hormone and IGF-1) prior to rescue by injectable somatostatin analogs, which is more likely to demonstrate a statistically significant result for octreotide capsules if we also achieve a statistically significant result as assessed by the primary endpoint. We expect to continue to evaluate the estimand-related secondary endpoints included in the statistical analysis plan for the CHIASMA OPTIMAL trial.

We anticipate that the FDA will review the totality of the data collected from the CHIASMA OPTIMAL trial, including both primary and secondary endpoints and whether the data collected are sufficiently robust to support the interpretability of these analyses, in determining whether to approve our NDA, if resubmitted, for the marketing and sale of octreotide capsules. There can be no assurance that the data collected from the CHIASMA OPTIMAL trial will be sufficient to support approval of our NDA, if resubmitted, for the marketing and sale of octreotide capsules.

We are heavily dependent on the regulatory approval and subsequent commercial success of octreotide capsules for the treatment of acromegaly in the United States and Europe, both of which may never occur.

We are a clinical-stage biopharmaceutical company with no products approved by regulatory authorities or available for commercial sale. As a result, our potential to generate future revenues is currently dependent upon our ability to obtain regulatory approval and achieve commercial success of octreotide capsules for the treatment of acromegaly in the United States and Europe. Our receipt of a CRL from the FDA to our NDA for octreotide capsules and the requirement to conduct an additional Phase 3 clinical trial to address the concerns raised in the CRL has resulted, and will continue to result, in a significant delay in our ability to commercialize octreotide capsules in the United States, if we are ever able to obtain U.S. regulatory approval at all.

Even if we receive regulatory approval, the timing of the commercial launch of octreotide capsules in the United States is dependent upon a number of factors, including, but not limited to, hiring and retaining sales and marketing personnel (especially since we terminated substantially all of our commercial personnel in June 2016), pricing and reimbursement timelines, the production of sufficient quantities of commercial drug product

Table of Contents

(especially since we indefinitely suspended all of our commercial manufacturing commitments during the second quarter of 2016) and implementation of a distribution infrastructure. In addition, the FDA may introduce significant restrictions to the label for octreotide capsules, if approved, in an effort to address the concerns it raised in the CRL and the End of Review meeting or to address findings in the CHIASMA OPTIMAL trial or the MPOWERED clinical trial. Any such restrictions or concerns about efficacy within the medical community could significantly impact market adoption and commercial performance of octreotide capsules, even if we are able obtain regulatory approval to commercialize in the United States in the future.

In addition, we have incurred and expect to continue to incur significant expenses and to utilize virtually all of our efforts and financial resources as we continue to pursue the approval of octreotide capsules in the United States and Europe. The success of octreotide capsules, if approved, will depend on several factors, including:

- execution of an effective sales and marketing strategy for the commercialization of octreotide capsules;
- acceptance by patients, the medical community and third-party payors;
- the incidence and prevalence of acromegaly in those markets in which octreotide capsules are approved;
- the prevalence and severity of side effects, if any, experienced with octreotide capsules;
- the availability, perceived advantages, cost, safety and efficacy of alternative treatments;
- our success in educating physicians and patients about the benefits, administration and use of octreotide capsules;
- successful implementation of our manufacturing processes and production of sufficient quantities of commercial drug product;
- maintaining compliance with regulatory requirements, including current good manufacturing practices, or cGMPs, and taking other measures satisfactory to the FDA; and
- obtaining and maintaining patent, trademark and trade secret protection and regulatory exclusivity and otherwise protecting our rights in our intellectual property portfolio.

We may also fail to develop future product candidates, especially since we terminated our research personnel in connection with the August 2016 restructuring plan. As a result, we continue to be dependent on the regulatory approval and successful commercialization of octreotide capsules, our development costs may increase and our ability to generate revenue or profits, or to raise additional capital could be impaired, all of which could result in further declines to our market value and stock price.

If we are not able to obtain required regulatory approvals for octreotide capsules, we will not be able to commercialize this product candidate and our ability to generate revenue or profits, raise future capital, or continue as a standalone business could be materially impaired.

In June 2015, we submitted an NDA to the FDA, for octreotide capsules for the maintenance therapy of acromegaly, which was accepted for filing to permit a substantive review. The FDA issued a CRL regarding our NDA on our PDUFA date of April 15, 2016, indicating that the NDA was not able to be approved during this review cycle and strongly recommending that we conduct a randomized, double-blinded, controlled trial. In the End of Review meeting, the FDA reiterated its strong recommendation for a randomized, double-blind and controlled trial.

In October 2015, the European Medicines Agency, or EMA, accepted the design, enrollment criteria and required duration of our second Phase 3 trial to evaluate the non-inferiority of octreotide capsules to injectable somatostatin analogs in adult patients with acromegaly. This clinical trial, which is referred to as MPOWERED and was initiated in March 2016, is an open-label, randomized, active-controlled study that is currently anticipated to enroll approximately 130 patients in the European Union, Russia, the United States and certain other countries. This clinical trial is currently designed to show comparative effectiveness as required by the EMA, to support submission of a marketing authorization application, or MAA, and potential approval. The FDA

Table of Contents

has advised us that positive data from the ongoing MPOWERED clinical trial, if obtained, will not be sufficient to address the concerns identified by the FDA in the CRL. Shortly following the receipt of this advice, we commenced the SPA process with FDA for the new Phase 3 CHIASMA OPTIMAL clinical trial. The FDA may never approve an octreotide capsules NDA, if resubmitted following the CHIASMA OPTIMAL trial, our ongoing MPOWERED Phase 3 clinical trial may not be successful, or acceptable to the EMA to support regulatory approval in Europe, the CRL or data produced from the CHIASMA OPTIMAL trial could adversely impact the EMA s review of our regulatory submission, and therefore we may never receive approval to market octreotide capsules in the United States, Europe or elsewhere.

Importantly, we expect that the safety and efficacy data generated in all of our clinical trials of octreotide capsules, including our completed phase 3 clinical trial, the CHIASMA OPTIMAL clinical trial and the MPOWERED clinical trial, to the extent such data is available at the time of filing, will be integrated into our planned NDA, if resubmitted, and planned MAA filing. While CHIASMA OPTIMAL has been designed to address the FDA s concerns in the CRL and the MPOWERED trial design has been accepted by the EMA, our ultimate success in the regulatory review process of each planned application for marketing approval could be impacted by the trial results from any of our clinical trials.

The research, testing, manufacturing, labeling, packaging, storage, approval, sale, marketing, advertising and promotion, export, import and distribution of drug products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, and these regulations differ from country to country and change over time. We are not permitted to market octreotide capsules in the United States until we receive approval of an NDA from the FDA, or in any foreign countries until we receive the requisite approvals in such countries. In the United States, the FDA generally requires the completion of nonclinical testing and clinical trials of each drug to establish its safety and efficacy and extensive pharmaceutical development to ensure its quality and other factors before an NDA is approved. Regulatory authorities in other jurisdictions impose similar requirements and may impose pricing restrictions. Of the large number of drugs in development, only a small percentage result in the submission of an NDA to the FDA and even fewer are approved for commercialization.

Other than the June 2015 submission of our NDA for octreotide capsules in acromegaly to the FDA, we have not yet submitted comparable applications to other regulatory authorities. If our development efforts for octreotide capsules, including our ability to obtain regulatory approval, are not successful for the acromegaly indication or are delayed, or if adequate demand for octreotide capsules are not generated, our business and ability to generate revenues will be materially harmed. Failure to obtain regulatory marketing approval of octreotide capsules in acromegaly will prevent us from commercializing the product candidate, which could raise significant concerns about our continued viability as a business.

The success of octreotide capsules will depend on the receipt of regulatory approval, and the issuance of such approvals is uncertain and subject to a number of risks, including the following:

- the FDA or comparable foreign regulatory authorities, institutional review boards, or IRBs, or ethics committees may disagree with the design or conduct of our clinical trials;

- we may not be able to provide acceptable evidence of octreotide capsules safety and efficacy;

the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA, the EMA or other regulatory agencies for marketing approval;

the dosing of octreotide capsules in a particular clinical trial may not be at an optimal level;

patients in our clinical trials may suffer adverse effects for reasons that may or may not be related to octreotide capsules;

the data collected from our clinical trials may not be sufficient to obtain regulatory approval in the United States or elsewhere;

Table of Contents

- the FDA or comparable foreign regulatory authorities may identify deficiencies with the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies, one of which was identified by the FDA in its CRL, or may later suspend or withdraw approval of our products;

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval; and

- even if we obtain marketing approval in one or more countries, future safety or other issues could result in the suspension or withdrawal of regulatory approval in such countries.

In particular, we cannot guarantee that regulators will agree with our assessment of the results of the clinical trials we have conducted to date, as was the case with the FDA s review of our completed Phase 3 clinical trial contained in the NDA, or that any current or future trials will be successful. The FDA, EMA and other regulators 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 clinical trials, or nonclinical or other studies, as the FDA strongly recommended in the CRL.

We have only limited experience in filing the applications necessary to gain regulatory approvals and have relied before, and expect to continue to rely, on consultants and third-party contract research organizations, or CROs, with expertise in this area to assist us in this process. Securing FDA approval requires the submission of extensive nonclinical and clinical data, information about product manufacturing processes and inspection of facilities and supporting information to the FDA for each therapeutic indication to establish a product candidate s safety and efficacy for each indication and manufacturing quality. Octreotide capsules or any future product candidates we may develop may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use with respect to one or all intended indications.

The process of obtaining regulatory approvals is expensive, often takes many years, if approval is obtained at all, and can vary substantially based upon, among other things, the type, complexity and novelty of the product candidates involved, the jurisdiction in which regulatory approval is sought and the substantial discretion of the regulatory authorities. Changes in the regulatory approval policy during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for a submitted product application may cause delays in the approval or rejection of an application or may result in future withdrawal of approval. Regulatory approval obtained in one jurisdiction does not necessarily mean that a product candidate will receive regulatory approval in all jurisdictions in which we may seek approval, but the failure to obtain approval in one jurisdiction may negatively impact our ability to seek approval in a different jurisdiction.

Our development, regulatory and commercialization strategy for octreotide capsules depends, in part, on published scientific literature and the FDA s prior findings regarding the safety and efficacy of approved products containing octreotide.

The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, added Section 505(b)(2) to the Federal Food, Drug, and Cosmetic Act, or Section 505(b)(2). Section 505(b)(2) permits the submission of an NDA where at least some of the information required for approval comes from investigations 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 or entity by or for whom the investigations were conducted. The FDA interprets Section 505(b)(2) to permit the applicant to rely, in part, upon published literature or the FDA s previous findings of safety and efficacy for

an approved product. The FDA also requires companies to perform additional clinical trials or measurements to support any difference from the previously approved product. The FDA may then approve the new product candidate for all or some of the label indications for which the listed drug has been approved, as well as for any new indication(s) sought by the Section 505(b)(2) applicant as supported by additional data. The label, however, may require all or some of the limitations, contraindications, warnings or precautions included in the listed drug s label, including a black box warning, or may require additional limitations, contraindications, warnings or precautions.

Table of Contents

We have designed our nonclinical and clinical programs to seek regulatory approval for octreotide capsules for registration filing in the United States using the FDA s 505(b)(2) regulatory pathway and using the hybrid application pathway, which is analogous to the 505(b)(2) regulatory pathway, in Europe. As such, our NDA in the United States relied, and if resubmitted following the CHIASMA OPTIMAL trial will continue to rely, and we intend that our MAA in Europe will rely, in part, on previous findings of safety and efficacy for an approved immediate-release injectable octreotide product and published scientific literature for which we have not received a right of reference. Even though we designed our development programs to take advantage of Section 505(b)(2) and the hybrid application pathway to support potential regulatory approval of octreotide capsules in the United States and Europe, the relevant regulatory authorities may require us to perform additional clinical trials or measurements to support approval over and above the clinical trials that we have already completed or initiated. The relevant regulatory authorities also may determine that we have not provided sufficient data to justify reliance on prior investigations involving the approved immediate-release injectable octreotide product.

In addition, notwithstanding the approval of many products by the FDA pursuant to Section 505(b)(2), in the past some pharmaceutical companies and others have objected to the FDA s interpretation of Section 505(b)(2). For example, parties have filed citizen petitions objecting to the FDA approving a Section 505(b)(2) NDA on scientific, legal and regulatory grounds. Scientific arguments have included the assertions that for the FDA to determine the similarity of the drug in the 505(b)(2) NDA to the listed drug, the FDA would need to reference proprietary manufacturing information or trade secrets in the listed drug s NDA; that it would be scientifically inappropriate for the FDA to rely on public or nonpublic information about the listed drug because it differs in various ways from the drug in the 505(b)(2) NDA; or that differences between the listed drug and the drug in the 505(b)(2) NDA may impair the latter s safety and effectiveness. Legal and regulatory arguments have included the assertion that Section 505(b)(2) NDAs must contain a full report of investigations conducted on the drug proposed for approval, and that approving a drug through the 505(b)(2) regulatory pathway would lower the approval standards. In addition, citizen petitions have made patent-based challenges against 505(b)(2) NDAs. For example, petitioners have asserted that the FDA should refuse to file a 505(b)(2) NDA unless it references a specific NDA as the listed drug, because it is most similar to the proposed drug, and provides appropriate patent certification to all patents listed for that NDA; or that when a 505(b)(2) NDA is pending before the FDA, but before it is approved, where the FDA approves an NDA for a drug that is pharmaceutically equivalent to the drug that is the subject of the 505(b)(2) NDA, then the FDA should require that the 505(b)(2) NDA be resubmitted referencing the approved NDA as the listed drug and certifying to the listed patents for that approved drug. However, if the FDA or EMA changes its interpretation of Section 505(b)(2) or the hybrid application pathway, or if the FDA s or EMA s interpretation is successfully challenged in court, this could delay or even prevent the FDA or EMA, as applicable, from approving any Section 505(b)(2) NDAs or hybrid application pathway MAAs that we submit. Such a result could require us to conduct additional testing and costly clinical trials, which could substantially delay or prevent the approval and launch of octreotide capsules for the treatment of acromegaly or any future product candidates we may develop.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome, and our current and future clinical trials may not be successful. Results of earlier studies and trials may not be predictive of future trial results, and approval in one jurisdiction may not be predictive of approval in other jurisdictions.

We initiated a second Phase 3 clinical trial of octreotide capsules in acromegaly called MPOWERED to support approval by the EMA. In the CRL and subsequent End of Review meeting minutes, the FDA strongly recommended that we conduct a randomized, double-blind and controlled trial, and introduced the concept of a placebo control as a design element that could potentially address some of the FDA s concerns. We acknowledged FDA s feedback contained in the CRL and in the End of Review meeting minutes, and are now conducting a third Phase 3 clinical trial, called the CHIASMA OPTIMAL trial, under the FDA s SPA procedures, which trial was initiated in September 2017. We may also consider clinical trials of octreotide capsules in indications other than acromegaly, assuming financing is

available to us and prior regulatory approvals of octreotide capsules in acromegaly are obtained. Clinical testing is expensive and can take many

Table of Contents

years to complete, and its outcome is inherently uncertain, and we will continue to be subject to these risks. Failure can occur at any time during the clinical trial process and results of future trials can adversely affect regulatory approvals previously received.

The results of nonclinical studies and prior clinical trials may not be predictive of the results of future clinical trials. The results of our completed clinical trials for octreotide capsules in acromegaly do not ensure that future clinical trials, including the MPOWERED Phase 3 trial required to support EMA approval, the CHIASMA OPTIMAL trial or other trials required by the FDA, or clinical trials for other indications, will also generate comparable results. Among other considerations, these trials may be designed in a way that is different from our completed clinical trials. For example, the EMA required that we use multiple time points in the Phase 3 clinical trial that we initiated in March 2016 rather than a single time point for the primary endpoint determination used for our initial Phase 3 clinical trial. The EMA agreed that we use the same cut off as used in our first Phase 3 clinical trial of IGF-1 < 1.3 times the upper limit of normal as the threshold for response while the FDA agreed that we use IGF-1 £ 1.0 times the upper limit of normal in the CHIASMA OPTIMAL trial. The fact that we have not used such endpoints previously for regulatory submissions introduces an additional level of uncertainty in the outcome of the MPOWERED and CHIASMA OPTIMAL Phase 3 clinical trials, or for other studies using this methodology for assessing the success of our product candidate. Further, the CHIASMA OPTIMAL trial design calls for the randomization of 50% of study patients to placebo capsules, the effect of which we cannot accurately estimate. We cannot provide assurance that the FDA or EMA will view the results as we do or that any future trials of octreotide capsules, including our current MPOWERED Phase 3 clinical trial in acromegaly to support regulatory approval in Europe or our CHIASMA OPTIMAL Phase 3 clinical trial in acromegaly to support regulatory approval in the United States, or clinical trials for other indications, if any, will achieve positive results. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through nonclinical studies and prior clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in prior trials.

Despite the results reported in earlier nonclinical studies and clinical trials for octreotide capsules for the treatment of acromegaly, any future clinical trial results of octreotide capsules may not be successful in acromegaly, or any other indication, if studied. A number of factors could contribute to a lack of favorable safety and efficacy results for octreotide capsules for acromegaly or other indications. For example, such trials could result in increased variability due to varying site characteristics, such as local standards of care, differences in evaluation period, and varying patient characteristics, including demographic factors and health status. If later-stage clinical trials do not produce favorable results, our ability to achieve regulatory approval of octreotide capsules for the treatment of acromegaly or other indications, and any other product candidates we may develop, may be adversely impacted.

Further, our NDA relied upon the FDA s 505(b)(2) regulatory pathway for octreotide capsules in acromegaly in the United States and we expect to rely on a similar hybrid application pathway for the MAA that we plan to submit in Europe. There can be no assurance that our clinical trials, or the clinical trials conducted by third parties, will demonstrate sufficient safety and efficacy for the FDA or EMA to approve octreotide capsules for the treatment of acromegaly or any other indication that may be specified in future NDA or MAA submissions. Even if we do obtain approval from the FDA for octreotide capsules for the treatment of acromegaly in the United States, we may not be successful in obtaining approval from the EMA or other regulatory authorities, or vice versa.

Any negative clinical results from, termination or suspension of, or delays in the commencement or completion of any ongoing or future trials of octreotide capsules for the treatment of acromegaly or for any additional indications, in the United States or other countries, or future clinical trials of product candidates we may develop could result in increased costs to us, delay or limit our ability to generate revenue, negatively impact our commercial prospects, cause our market value and stock price to fall and jeopardize our viability as a business.

Delays in the completion of the Phase 3 MPOWERED clinical trial we initiated in March 2016 to support marketing approval of octreotide capsules in acromegaly in Europe, the CHIASMA OPTIMAL trial which we initiated in September 2017 to support regulatory approval of octreotide capsules in the United States, the clinical

Table of Contents

trials of octreotide capsules for other indications we may pursue, if conducted, or any future clinical trials we may conduct for other product candidates we may develop, or negative findings in those trials, could significantly affect our product development costs or our ability to commercialize octreotide capsules. For example, in October 2015, the EMA required us to revise our protocol for our MPOWERED Phase 3 clinical trial to extend the control period from six months to nine months. The final protocol accepted by EMA therefore dictated that additional time will be needed to complete our second Phase 3 clinical trial of octreotide capsules. We do not know whether the MPOWERED Phase 3 trial or the CHIASMA OPTIMAL Phase 3 trial will be completed on schedule, if at all, or will be successful. In light of the FDA s position that the MPOWERED clinical trial will not be sufficient to address the concerns in the CRL, in late 2016 we modified certain elements of the MPOWERED trial in an effort to preserve patients, sites and other resources necessary to conduct the CHIASMA OPTIMAL Phase 3 trial. The modifications to the MPOWERED trial will delay the expected timing of an MAA filing with the EMA, which we previously estimated to occur in 2019, and we now expect top-line data from the MPOWERED study in 2020. The completion of the MPOWERED or CHIASMA OPTIMAL Phase 3 trials or other clinical trials that may be conducted can be delayed for a number of other reasons, including delays related to:

- the FDA, the EMA or any other relevant regulatory authority failing to grant permission to proceed and placing the clinical trial on hold;

- patient enrollment and variability in the number and types of patients available for clinical trials, which is particularly challenging for orphan indications, and our CHIASMA OPTIMAL trial may be particularly difficult to enroll given the placebo-controlled design as well as other ongoing clinical trials in adult acromegaly patients;

- a facility manufacturing octreotide acetate, octreotide capsules, placebo capsules or any other product candidate we may develop being found deficient in its processes, as the FDA noted in its CRL to our NDA, or ordered by the FDA, EMA or other government or regulatory authorities to temporarily or permanently shut down due to violations of cGMP requirements or other applicable requirements, or cross-contaminations of product candidates in the manufacturing process;

- any changes to our manufacturing process that may be necessary or desired or a failure to successfully manufacture qualifying clinical trial supplies of oral octreotide capsules or placebo;

- patients choosing an alternative treatment for acromegaly or any of the indications for which we may develop octreotide capsules or potential product candidates, or participating in competing clinical trials;

- difficulty in maintaining contact with patients after treatment, resulting in incomplete or missing data;

- patients experiencing drug-related adverse effects;

reports from clinical testing on similar technologies and products raising safety and/or efficacy concerns;

third-party clinical investigators losing their licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or employing methods that are inconsistent with the clinical trial protocol, good clinical practice, or GCP, requirements, or other third parties not performing data collection and analysis in a timely or accurate manner;

inspections of clinical trial sites by the FDA, EMA or other regulatory authorities finding regulatory violations that require us to undertake corrective action, result in suspension or termination of one or more sites or the imposition of a clinical hold on the entire trial, or that prohibit us from using some or all of the data in support of our marketing applications;

third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or any of the data produced by such contractors in support of our marketing applications;

Table of Contents

one or more IRBs or ethics committees refusing to approve, suspending or terminating the study at an investigational site, precluding enrollment of additional patients, or withdrawing its approval of the trial;

reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

deviations of the clinical sites from trial protocols or dropping out of a trial;

delays in adding new clinical trial sites;

the inability of the CRO to execute any clinical trials for any reason;

the inability to enroll patients who participated in prior clinical trials in our current or planned clinical trials; or

government or regulatory delays or clinical holds requiring suspension or termination of a trial.

Product development costs for octreotide capsules in acromegaly or any other future indications we may pursue or for product candidates we may develop in the future will increase if we have delays in testing or approval, such as the delay in approval of octreotide capsules due to the CRL to our NDA, or if we need to perform more or larger clinical studies than planned. If we experience delays in the completion of, or if we, the FDA, other regulatory authorities, IRBs or other reviewing entities, or any of our clinical trial sites suspend or terminate any of our clinical trials of octreotide capsules for any indication, its commercial prospects may be harmed and our ability to generate product revenues will be delayed. Any delays in completing our clinical trials will increase our costs, slow down our development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial or even withdrawal of regulatory approval of octreotide capsules for any indication. In addition, if one or more clinical trials are delayed, our competitors may be able to bring products to market before we do, and the commercial viability of octreotide capsules could be significantly reduced.

Changes in regulatory requirements and guidance may also occur, and we may need to amend clinical trial protocols submitted to applicable regulatory authorities to reflect these changes. Amendments may require us to resubmit clinical trial protocols to IRBs or ethics committees for re-examination, which may impact the costs, timing or successful completion of a clinical trial.

The FDA s and other regulatory authorities policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of octreotide capsules and any future product candidates we may develop. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, and we may not achieve or sustain profitability, which would harm our business, prospects, financial condition and results of operations.

If we are required to conduct additional clinical trials or other studies with respect to octreotide capsules or any future product candidates we may develop beyond those that we may propose to conduct, or if we are unable to successfully complete our clinical trials or other studies, we may be delayed in obtaining regulatory approval of octreotide capsules and any future product candidates we may develop, we may not be able to obtain regulatory approval at all or we may obtain approval of indications that are not as broad as intended. Our product development costs will also increase if we experience delays in testing or approvals, and we may not have sufficient funding to complete the testing and approval process for octreotide capsules or any future product

Table of Contents

candidates we may develop. Significant clinical trial delays could allow our competitors to bring products to market before we do and impair our ability to commercialize our products if and when approved. If any of this occurs, our business would be harmed.

We may find it difficult to enroll patients in our clinical trials, in particular with respect to octreotide capsules and any other product candidates that we may pursue, which could delay or prevent clinical trials of octreotide capsules and any future product candidates we may develop and potentially harm our business.

Identifying and qualifying patients to participate in clinical trials of octreotide capsules and any future product candidates we may develop is critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing octreotide capsules and any future product candidates we may develop as well as completion of required follow-up periods. If patients are unable or unwilling to participate in our clinical trials for any reason, including if patients choose to enroll in competitive clinical trials for similar patient populations or they are unwilling to enroll in a clinical trial with a placebo-controlled design, such as our CHIASMA OPTIMAL trial, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of octreotide capsules and any future product candidates we may develop may be delayed. These delays could result in increased costs, and we may not have sufficient capital on hand or the ability to raise additional capital to cover such costs, delays in advancing octreotide capsules or any future product candidates we may develop, delays in testing the effectiveness of future product candidates, if any, or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial, to complete our clinical trials in a timely manner. In particular, the conditions for which we may evaluate octreotide capsules are orphan diseases with limited patient pools from which to draw for clinical trials. The eligibility criteria of our clinical trials will further limit the pool of available trial participants. For example, while we are enrolling patients in Russia, Europe and other countries, we are not permitted to enroll patients from our prior clinical trials in our ongoing Phase 3 clinical trial to support MAA submission and approval in Europe. The same limitation is true for our CHIASMA OPTIMAL trial. Further, in light of the FDA s position that the MPOWERED clinical trial will not be sufficient to address the concerns in the CRL, we have modified certain elements of the MPOWERED trial in an effort to preserve patients, sites and other resources necessary to conduct the CHIASMA OPTIMAL Phase 3 trial. Further, the issuance of the CRL by the FDA may negatively impact physician or patient attitudes towards octreotide capsules which could significantly delay enrollment in both MPOWERED and CHIASMA OPTIMAL trials or any future trials. In addition, conducting a randomized, double-blind and controlled trial in the United States, as strongly recommended by the FDA in the CRL and End of Review meeting minutes, and as is part of the design of our CHIASMA OPTIMAL trial being conducted per a SPA reached with the FDA in August 2017, may be particularly challenging as we believe it may be difficult to identify patients with acromegaly willing to enroll in a trial with this design. We expect to conduct the MPOWERED and CHIASMA OPTIMAL Phase 3 trials simultaneously, and as such, we will have two active clinical trials competing for the same or similar pools of patients and enrollment in either trial, or both trials, could be negatively impacted.

Patient enrollment is affected by factors including the:

- severity of the disease under investigation;
- design of the clinical trial protocol;

size and nature of the patient population;

eligibility criteria for the trial in question;

perceived risks and benefits of the product candidate under trial;

possibility of receiving placebo rather than active drug in certain controlled trials, such as in the CHIASMA OPTIMAL trial;

Table of Contents

possibility of being randomized back to current injectable therapies, such as in the MPOWERED trial, or rescued back to current injectable therapies following a loss of biochemical and symptom control, such as in the CHIASMA OPTIMAL trial;

proximity and availability of clinical trial sites for prospective patients;

availability of competing therapies and clinical trials;

perceptions of patients and healthcare providers as to the potential advantages 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;

efforts to facilitate timely enrollment of patients in clinical trials;

patient referral practices of physicians; and

ability to monitor patients adequately during and after treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials or our clinical trials produce incomplete data, we may be forced to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business. We could encounter delays if physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of octreotide capsules and any future product candidates we may develop in lieu of prescribing existing treatments that have established safety and efficacy profiles. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA, the EMA or other regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including the:

difficulty in establishing or managing relationships with CROs and physicians;

different requirements and standards for conducting clinical trials;

inability to locate qualified local consultants, physicians and partners; and

potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatments.

Even if we receive regulatory approval of octreotide capsules for acromegaly, we may still face future development and regulatory challenges that could inhibit or preclude our ability to commercialize octreotide capsules for any

indication.

Even if we obtain regulatory approval of octreotide capsules for the treatment of acromegaly, and other indications we may pursue, or any other product candidates we may develop, they will be subject to ongoing requirements by the FDA and comparable foreign regulatory authorities governing manufacturing, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. If approved, the safety profile of octreotide capsules and any future product candidates we may develop will continue to be closely monitored by the FDA and comparable foreign regulatory authorities after approval. If new safety information becomes available after approval of octreotide capsules and any future product candidates we may develop, the FDA or comparable foreign regulatory authorities may require labeling changes or establishment of a Risk Evaluation and Mitigation Strategy, or REMS, or similar strategy, impose significant restrictions on our product candidates, indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. For example, the label ultimately approved for octreotide capsules, if it achieves marketing approval, may include restrictions on use, which could limit the marketability of octreotide capsules and impair our ability to have octreotide capsules gain market acceptance. If we do not receive approval of octreotide capsules for the treatment of acromegaly, there would be significant doubts about our viability as a standalone business.

Table of Contents

In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP and other regulations. If we or a regulatory authority discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, we may recall or withdraw the product from the market or a regulatory authority may impose restrictions on that product, the manufacturing facility or us, including requiring suspension of manufacturing. If we, our potential products or the manufacturing facilities for our potential products fail to comply with applicable regulatory requirements, a regulatory authority may, among other things:

- issue warning letters or untitled letters;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products, or request that we initiate a product recall.

The occurrence of any event or penalty described above may inhibit or preclude our ability to commercialize octreotide capsules, if approved, and any future product candidates we may develop and generate revenue.

We face substantial competition from larger companies with considerable resources that already have somatostatin analogs available in the market, and they or others may also discover, develop or commercialize additional products before or more successfully than we do.

Our industry is highly competitive and subject to rapid and significant technological change as researchers learn more about diseases and develop new technologies and treatments. Our potential competitors include primarily large

pharmaceutical, biotechnology and specialty pharmaceutical companies. If approved, we expect octreotide capsules will face competition from established drugs and major brand names and also generic versions of these products. Key competitive factors affecting the commercial success of octreotide capsules and any other product candidates we may develop are likely to be efficacy, safety and tolerability profile, reliability, convenience of administration, price and reimbursement and effectiveness of our promotional activities. For example, physicians may choose not to prescribe octreotide capsules, if approved, because a lower percentage of patients met the criteria for response in our first Phase 3 clinical trial after treatment with octreotide capsules compared to their baseline response rates on injectable therapy or if similar data are produced by the CHIASMA OPTIMAL or MPOWERED clinical studies. Competition could also force us to lower prices or could result in reduced sales.

The standards of care for patients suffering from acromegaly all involve injectable therapies, other than cabergoline, an oral agent used for the treatment of mild acromegaly. Novartis markets octreotide LAR, which is administered monthly and intramuscularly using a large gauge needle. Ipsen markets lanreotide, another long-acting analog of somatostatin, like octreotide, which is administered monthly using a deep subcutaneous injection. Pfizer markets pegvisomant daily injections and Novartis also markets pasireotide LAR, which is another somatostatin analog administered via intramuscular injection. We are aware of other companies involved

Table of Contents

in early-stage nonclinical and clinical studies of similar somatostatin analogs. Most notably, Camurus AB, in partnership with Novartis, is developing CAM2029, a subcutaneous octreotide depot for the potential treatment of neuroendocrine tumors and acromegaly. Published reports indicate that Camurus AB intends to communicate updated project time-lines for the start of their Phase 3 program in mid-2018 which may directly compete with us for the limited number of acromegaly patients willing to participate in our current clinical trials. MidaTech Pharma PLC also recently announced plans to conduct its first in human study of Q-Octreotide (MTD201), Midatech s injectable treatment for acromegaly built on its Q-Sphera sustained release platform technology. Assuming positive clinical data, Midatech anticipates a launch as early as 2020. In October 2017, Crinetics Pharmaceuticals, Inc. announced the initiation of a Phase 1, double-blind, randomized, placebo-controlled, single- and-multiple-dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of CRN00808 in healthy volunteers. CRN00808 is a nonpeptide somatostatin agonist designed to be taken orally. In May 2017, Dauntless Pharmaceuticals, Inc., a privately held biopharmaceutical company announced positive results from its two-part, Phase 1 pharmacokinetic/pharmacodynamic study evaluating DP1038, a novel formulation of octreotide acetate for intranasal administration. If any or a combination of CAM2029, MTD201, CRN00808 or DP1038 and our octreotide capsules receive regulatory approval in a similar timeframe, we may face difficulties with our commercial launch with one or more new competitive products launching simultaneously or in similar timeframes.

Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. These companies also have long-established relationships within the medical and patient community, including patients, physicians, nurses and commercial third-party payors and government payors. Our ability to compete successfully will depend largely on our ability to:

- develop our product candidate and demonstrate that it is competitive with or superior to other products on the market;
- obtain required regulatory approvals;
- adequately communicate the benefits of octreotide capsules, if approved;
- attract and retain qualified personnel;
- obtain and maintain patent and/or other proprietary protection for octreotide capsules and any future product candidates we may develop; and
- in certain geographies, obtain collaboration arrangements to develop and commercialize octreotide capsules and any future product candidates we may develop.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval of drugs and achieving widespread market acceptance. Our competitors drugs

may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render octreotide capsules or any future product candidates we may develop obsolete or non-competitive before we can recover the expenses of developing and commercializing octreotide capsules or any future product candidates we may develop. Our competitors may also obtain FDA or other regulatory approval of their products more rapidly than we may obtain approval of ours. We anticipate that we will face intense and increasing competition as new drugs enter the market and more advanced technologies become available. For example, a competitor could develop another oral formulation of a somatostatin analog or other technology that could make administration of peptide-based therapies more convenient. If we are unable to compete effectively, our opportunity to generate revenue from the sale of octreotide capsules or any future product candidates we may develop, if approved, could be impaired.

Table of Contents

The number of patients suffering from acromegaly is small, and has not been established with precision. Our assumptions and estimates regarding prevalence may be wrong. If our octreotide capsules product candidate is approved for sale, and the actual number of patients in the applicable market is smaller than we estimate, our revenue could be adversely affected, possibly materially.

There are an estimated 69,000 individuals with acromegaly worldwide. The U.S. National Institutes of Health, or NIH, estimates that there are roughly 20,000 individuals with acromegaly in the United States, based on its published prevalence of an estimated 60 cases per million. In thirteen studies of acromegaly prevalence since 1980, an average of approximately 75 cases per million was determined, suggesting roughly 24,000 individuals with acromegaly in the United States. However, data presented at the Endocrine Society s Annual Meeting in 2015 suggest that pituitary tumors may be more prevalent than previously thought, and that the global prevalence of acromegaly may be higher, between 85 and 118 cases per million people. NIH also cites an annual incidence of three to four new cases per million each year. We believe that approximately 8,000 adult acromegaly patients are chronically treated with somatostatin analogs in the United States. However, there is no guarantee that these estimates are correct. The number of patients with acromegaly, in particular the number of patients for whom our octreotide capsules product, if approved, is approved for use, could actually be significantly lower than these estimates.

We believe that the actual size of the total addressable acromegaly market in those markets in which our octreotide capsules product is approved, if at all, will be determined only after we have substantial history as a commercial company. If the total addressable market for our products is smaller than we expect, our revenue could be adversely affected, possibly materially.

Even if we receive regulatory approval of octreotide capsules, it may not achieve an adequate level of acceptance by physicians, patients and third-party payors and government payors, and we may not generate sufficient revenue or be able to achieve or sustain profitability.

The commercial success of octreotide capsules, if approved, will depend in large part on the willingness of physicians to prescribe them to their patients. Octreotide capsules, if approved, will compete against products that have achieved broad recognition and acceptance among medical professionals. In order to achieve an acceptable level of prescriptions for octreotide capsules, if approved, we must be able to meet the needs of both the medical community and patients with respect to cost, efficacy and other factors. The degree of market acceptance of octreotide capsules, if approved, will depend on a number of factors, including:

- the clinical safety, efficacy, tolerability and other factors regarding octreotide capsules relative to injectable somatostatin analogs and any other treatments available at the time;
- the relative convenience, number of capsules that need to be taken, requirement to fast before and after each dose of octreotide capsules, and other factors affecting the ease of administration;
- the prevalence and severity of any adverse effects;
- the willingness of physicians to prescribe octreotide capsules and of the target patient population to try new therapies;

the introduction of any new products that may in the future become available to treat indications for which octreotide capsules may be approved;

changes in the clinical or economic profiles of alternative treatments;

new procedures or methods of treatment that may reduce the incidences of any of the indications in which octreotide capsules may show utility;

pricing and cost-effectiveness;

the effectiveness of our or any future collaborators sales and marketing, as well as disease education and awareness programs;

Table of Contents

limitations or warnings contained in labeling approved by the FDA or comparable foreign regulatory authorities;

our ability to obtain and maintain sufficient third-party coverage and adequate reimbursement from government health care programs, including Medicare and Medicaid, private health insurers and other third-party payors;

the willingness of patients to pay out-of-pocket in the absence of third-party coverage or reimbursement;

competitor activities; and

our ability to reliably manufacture and supply octreotide capsules.

In addition, even if we obtain regulatory approvals, the timing or scope of any approvals may prohibit or reduce our ability to commercialize octreotide capsules successfully. For example, if the approval process takes too long, which is a greater likelihood as a result of the CRL from the FDA to our NDA and our plans to conduct the CHIASMA OPTIMAL Phase 3 trial prior to any resubmission of our NDA, we may miss market opportunities and give other companies the ability to develop competing products or establish market dominance. Any regulatory approval we ultimately obtain may be limited or be subject to restrictions or post-approval commitments that render octreotide capsules not commercially viable. For example, regulatory authorities may approve octreotide capsules for more limited indications than we request, may limit approved usage to narrower patient populations, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve octreotide capsules with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that indication. Any of the foregoing scenarios could harm the commercial prospects for octreotide capsules.

Even if octreotide capsules are approved, they may not achieve an adequate level of acceptance by physicians, healthcare payors and patients, and we may not generate sufficient revenue or be able to achieve or sustain profitability. Our revenue and profitability may also be delayed during the period of time when commercial third-party payors and government payors are becoming familiar with octreotide capsules and patients are transitioning from injected alternatives to octreotide capsules. Our efforts to educate the medical community, patients and third-party payors on the benefits of octreotide capsules may require significant resources and may never be successful. Even if we are able to demonstrate and maintain a competitive advantage over our competitors, if the market for octreotide decreases, we may not generate sufficient revenue.

Due to our corporate restructuring in June 2016, we no longer have a sales and marketing organization and, as a company, have not commercialized any products. If we are able to secure regulatory approval for octreotide capsules in acromegaly, but are unable to establish effective sales and marketing capabilities in the United States and access them in Europe and other international markets, we may not succeed in commercializing octreotide capsules.

As a result of our June 2016 restructuring action, we essentially no longer have sales and marketing personnel. Based upon feedback provided by the FDA in the CRL and End of Review meeting minutes, as well as through the SPA process, new or additional data will be required before the FDA would consider U.S. regulatory approval for the marketing and sale of octreotide capsules in acromegaly, which requires that we conduct the CHIASMA OPTIMAL Phase 3 trial and possibly additional clinical trials.

Even if we are able to obtain regulatory approval, we cannot guarantee when that will occur or whether we will be successful in marketing octreotide capsules in the United States or any other jurisdiction. If we are not successful in recruiting of sales and marketing personnel on a timely basis or rebuilding a sales and marketing infrastructure, or if we do not successfully enter into appropriate collaboration arrangements, we will have difficulty commercializing octreotide capsules, if approved, which could harm our business, operating results and financial condition.

Table of Contents

If pursued by us, expansion of our business into the European Union and other international markets will require significant management attention and additional financial resources. We may explore commercializing octreotide capsules in Europe and other international markets by entering into collaboration agreements with other biopharmaceutical companies, and we may not be successful in entering into these collaboration agreements. In the event that we do enter into such agreements, we may have limited or no control over the sales, marketing and distribution activities of these third parties. Additional factors and risks that may inhibit our efforts to commercialize octreotide capsules in foreign markets include:

- our inability to directly control commercial activities because we are relying on third parties, should we enter into third-party collaborations;
- varying pricing in different foreign markets, which could adversely affect pricing in other countries;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer collection times for accounts receivable;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries, and related prevalence of generic alternatives to therapeutics;
- foreign currency exchange rate fluctuations;
- our customers ability to obtain adequate reimbursement for octreotide capsules in foreign markets, either at all or at prices that exceed our costs; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of octreotide capsules could also be adversely affected by the imposition of governmental price controls, political and economic instability, trade restrictions and changes in tariffs.

Our future revenues may depend heavily on the success of the efforts of these third parties. We may not be able to establish a commercial operation in a cost-effective manner or realize a positive return on this investment, even with the assistance of one or more third-party collaborators, should we choose to enter into such an arrangement. In addition, we will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain sales and marketing personnel.

If we or third-party collaborators are not successful in recruiting sales and marketing personnel or in building a sales and marketing infrastructure, or if we do not successfully enter into additional collaboration arrangements with third parties, we may not be able to successfully commercialize octreotide capsules or any future product candidates we may develop in foreign markets, which could impair our business, operating results and financial condition.

Even with the potential assistance of third-party collaborators, we may not be successful in establishing a commercial operation in foreign markets for numerous reasons, including, but not limited to, failing to attract, retain and motivate the necessary skilled personnel and failing to develop a successful marketing strategy. Failure to establish a commercial operation in foreign markets will have a negative outcome on our ability to commercialize octreotide capsules and generate revenue.

Table of Contents

Additionally, if approved for marketing in one or more countries, we and/or our potential third-party collaborators may encounter unexpected or unforeseen delays in establishing our commercial operations that delay the commercial launch in these countries. These delays may increase the cost of and the resources required for successful commercialization of octreotide capsules both in the United States and internationally. We do not have any experience in a commercial launch in the United States, Europe or elsewhere.

Due to our corporate restructuring in 2016, we no longer have a medical affairs organization and, if we are unable to establish effective medical affairs capabilities in the United States and build or access them in Europe and other international markets, our business may suffer.

As a result of our June 2016 restructuring action, we generally no longer have a medical affairs organization. Medical affairs personnel are responsible for a number of key activities within biopharmaceutical companies, which include, but are not limited to, providing expert advice to other functions within the organization, advising on medical education activities, reviewing promotional and non-promotional communications, supporting medical and scientific publications, reviewing grants for third-party continuing medical education events, and providing an important scientific point of contact for physicians and scientists who seek to partner with us or better understand our science.

Failure to successfully execute these activities could harm our business in the following ways:

- our reputation among key physicians and scientists in acromegaly and other disease areas of interest to us may suffer;
- we may not be able to secure the advice and feedback of outside experts to help advance our knowledge and understanding of complex scientific and medical issues;
- our commercial and corporate functions may not receive adequate medical and scientific information in the creation of their external communications, which could lead to inaccurate information being disseminated about us, our product candidates, our disease areas of interest, or our other scientific endeavors;
- our promotional, non-promotional, grants, and medical events review processes may not provide an effective control to ensure compliance with applicable laws, regulations and standards; and
- we may not successfully interact with European or other ex-U.S. healthcare professionals and scientists who could help us execute plans for expansion into Europe or other international markets.

Even if we obtain marketing approval of octreotide capsules or any future product candidates we may develop, we will be subject to ongoing obligations and continued regulatory review, including with respect to the advertising and promotion of any product candidate that obtains approval.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by, among others, the FDA, the Department of Justice, or DOJ, the Office of Inspector General of the Department of Health and Human Services, or HHS, state attorneys general, members of Congress and the public, as well as by foreign regulatory authorities in the countries in which we commercialize octreotide capsules. Even if

octreotide capsules are being marketed, the manufacture and marketing of octreotide capsules will be subject to ongoing regulation, including compliance with cGMPs, adverse event reporting requirements, guidance regarding the provision of reimbursement support and patient services, and general prohibitions against promoting products for unapproved or off-label uses. Violations of these ongoing regulations are subject to enforcement letters, inquiries and investigations, and civil and criminal sanctions by the FDA or other government agencies. Government investigation of these issues itself typically requires the expenditure of significant resources and can generate negative publicity, which could harm our business. Additionally, advertising and promotion of any product candidate that obtains approval outside of the United States will be heavily scrutinized by comparable foreign regulatory authorities.

Table of Contents

In the United States, engaging in impermissible promotion of our drug products for off-label uses can also subject us to false claims litigation under federal and state statutes, and other litigation and/or investigation, which can lead to significant administrative civil and criminal penalties and fines and agreements that materially restrict the manner in which we promote or distribute our drug products. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government decides to intervene and prevails in the lawsuit, the individual will share in any fines or settlement funds. In recent years, these False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to substantial civil and criminal settlements based on certain sales practices promoting off-label drug uses. This increasing focus and scrutiny has increased the risk that a pharmaceutical company will have to defend a false claim action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations, and be excluded from the Medicare, Medicaid and other federal and state healthcare programs, among other penalties. If we do not lawfully promote our approved products, we may become subject to such litigation and/or investigation and, if we are not successful in defending against such actions, those actions could compromise our ability to become profitable.

The manufacture and packaging of pharmaceutical products such as octreotide capsules are subject to FDA requirements and those of similar foreign regulatory bodies. If we or our third-party manufacturers fail to satisfy these requirements, our product development and commercialization efforts may be harmed.

The manufacture and packaging of pharmaceutical products, such as octreotide capsules, if approved, are regulated by the FDA and similar foreign regulatory bodies and must be conducted in accordance with the FDA s cGMP and comparable requirements of foreign regulatory bodies. There are a limited number of manufacturers that operate under these cGMP regulations who are both capable of manufacturing octreotide capsules and willing to do so. Failure by us or our third-party manufacturers to comply with applicable regulations or requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delays, suspension or withdrawal of approvals, seizures or voluntary recalls of product, operating restrictions and criminal prosecutions, any of which could harm our business. The same requirements and risks are applicable to the suppliers of the key raw material used to manufacture the active pharmaceutical ingredient, or API, for octreotide capsules. For example, in its CRL, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval of our NDA for octreotide capsules. Although we were informed that the supplier received an Establishment Inspection Report, or EIR, from the FDA, indicating that the FDA has concluded its inspection of the supplier and as of the date of its report considers outstanding deficiencies resolved, we expect that our suppliers will be subject to additional regulatory inspections in the future, including in connection with the FDA s review of any NDA we may submit in the future, if any, seeking approval of octreotide capsules in acromegaly. There can be no assurances that our suppliers will pass all future inspections, the failure of which could result in delays to our ability to receive regulatory approval for octreotide capsules.

Changes in the manufacturing process or procedure, including a change in the location where the product is manufactured or a change of a third-party manufacturer, may require prior FDA review and approval of the manufacturing process and procedures in accordance with the FDA s cGMPs. Any new facility is subject to a pre-approval inspection by the FDA and would again require us to demonstrate product comparability to the FDA. There are comparable foreign requirements. This review may be costly and time consuming and could delay or prevent the launch of a product.

Furthermore, in order to obtain approval of our product candidates, including octreotide capsules, by the FDA and foreign regulatory agencies, we will be required to consistently produce the API and the finished product in

commercial quantities and of specified quality on a repeated basis and document our ability to do so. Each of our potential API suppliers will likely use a different method to manufacture API, which has the potential to increase

Table of Contents

the risk to us that our manufacturers will fail to meet applicable regulatory requirements. If approved, we will also need to complete required testing on the finished product in the packaging we propose for commercial sales. This includes testing of stability, measurement of impurities and testing of other product specifications by validated test methods. If the FDA does not consider the result of the process validation or required testing to be satisfactory, commercial supply after NDA approval, if obtained, and launch may be delayed.

The FDA and similar foreign regulatory bodies may also implement new requirements, or change their interpretation and enforcement of existing requirements, for manufacturing, packaging or testing of products at any time. If we are unable to comply, we may be subject to regulatory, civil actions or penalties which could harm our business.

If we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, the commercialization of octreotide capsules and any future product candidates we may develop may be delayed, our business will be harmed and we may not have sufficient resources to continue as a standalone company.

We estimate for planning purposes the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of clinical trials, the submission of regulatory filings, or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the initiation or completion of an ongoing clinical trial, receipt of marketing approval, or a commercial launch of a product. The achievement of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions which may cause the timing of achievement of the milestones to vary considerably from our estimates, including:

- our available capital resources or capital constraints we experience;
- the rate of progress, costs and results of our clinical trials and research and development activities, including the extent of scheduling conflicts with participating clinicians and collaborators, and our ability to identify and enroll patients who meet clinical trial eligibility criteria;
- our strategic decisions on trial design and modifications thereto in an effort to preserve patients, sites and other resources necessary to conduct the CHIASMA OPTIMAL Phase 3 trial and MPOWERED Phase 3 trial and produce data packages that could be suitable for submission in both the United States and the European Union;
- our receipt of approvals by the FDA and other regulatory agencies and the timing thereof;
- other actions, decisions or rules issued by regulators;
- our ability to access sufficient, reliable and affordable supplies of compounds used in the manufacture of octreotide capsules and any future product candidates we may develop;

the efforts of our collaborators and the success of our own efforts with respect to the commercialization of our products; and

the securing of, costs related to, and timing issues associated with product manufacturing as well as sales and marketing activities.

If we fail to achieve announced milestones in the timeframes we announce and expect, the commercialization of octreotide capsules, if approved, and any future product candidates we may develop may be delayed and our business and results of operations may be harmed.

Table of Contents

Octreotide capsules and other products we may develop, if approved, may not be commercially viable if we fail to obtain coverage and an adequate level of reimbursement for these products from governmental payors, including Medicare and Medicaid programs, private insurers, and other third-party payors. The market for octreotide capsules and other products we may develop may also be limited by the indications for which their use may be reimbursed.

The availability of coverage and adequate levels of reimbursement by governmental and other third-party payors will affect the market for octreotide capsules, if approved, and subsequent products that we may develop, if any. These third-party payors continually attempt to contain or reduce the costs of health care, such as by challenging the prices charged for medical products and services and by applying value assessments to clinical outcomes using different safety and efficacy standards than used for marketing approval by the FDA and the EMA.

In the United States, in the event that octreotide capsules are approved, we will seek to obtain reimbursement for octreotide capsules from third-party payors. In recent years, through legislative and regulatory actions, the federal government has made substantial changes to various payment systems under the Medicare program. Comprehensive reforms to the U.S. healthcare system were enacted in 2010 with the passage of the Affordable Care Act, or the ACA. These reforms could significantly reduce payments from Medicare and Medicaid over the next 10 years. Reforms or other changes to these payment systems, including modifications to the conditions on qualification for payment, bundling of payments or the imposition of enrollment limitations on new providers, may change the availability, methods and rates of reimbursements from governmental payors, private insurers and other third-party payors for octreotide capsules and any other potential products we may pursue. Some of these changes and proposed changes could result in reduced reimbursement rates for octreotide capsules and any other potential products we may pursue, which would adversely affect our business strategy, operations and financial results.

In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a product from a governmental or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high.

We expect that private insurers will consider the efficacy, cost effectiveness and safety of octreotide capsules, if approved, in determining whether to provide reimbursement for octreotide capsules and at what level. Obtaining these additional approvals for reimbursement can be a time-consuming and expensive process. Even if we receive regulatory approval to market octreotide capsules, our business would be harmed if we do not receive approval of reimbursement of octreotide capsules from third-party payors on a timely or satisfactory basis. Medicare does not cover particular drugs if it determines that they are not reasonable and necessary for its beneficiaries. Limitations on coverage could also be imposed at the local Medicare carrier level or by fiscal intermediaries. Our business could be harmed if Medicare, local Medicare carriers or fiscal intermediaries were to make such a determination and deny or limit the reimbursement of octreotide capsules.

Our business could also be harmed if governments, private insurers, Medicare, Medicaid or other reimbursing bodies or payors limit the indications for which octreotide capsules will be reimbursed to a smaller set than we believe it is safe and effective in treating, or establish a limitation on the frequency with which octreotide capsules may be administered that is less often than we believe would be safe and effective, or establish a limitation on dose that is lower than we believe would be safe and effective. In addition, even if we receive regulatory approval, the FDA may introduce significant restrictions to the label for octreotide capsules in an effort to address certain concerns raised in

the CRL, End of Review meeting or the FDA s review of the CHIASMA OPTIMAL trial or any current or future clinical trials we may conduct. Any such restrictions or potential reservations about efficacy expressed by the FDA or within the medical community could significantly impact reimbursement, market adoption and commercial performance of octreotide capsules.

Table of Contents

We expect to experience pricing pressures in connection with the sale of octreotide capsules and any future product candidates we may develop, if required regulatory approvals are obtained, due to healthcare reforms, as well as the trend toward programs aimed at reducing health care costs, the increasing influence of health maintenance organizations, additional legislative proposals, and the economic health of companies. If coverage and reimbursement for our products are unavailable, or are limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

In Europe and many other foreign countries, the pricing of prescription pharmaceuticals is subject to governmental control, and each country has a different reviewing body that evaluates reimbursement dossiers submitted by holders of marketing authorizations for new drugs. That governing body then makes recommendations as to whether or not the drug should be reimbursed. In these countries, pricing negotiations with governmental authorities can take 12 months or longer after the receipt of regulatory approval. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate, such as octreotide capsules, to other available therapies.

The longer term growth of our business depends on our efforts to expand the approved uses of octreotide capsules beyond acromegaly, if approved, and leverage our TPE platform to expand our portfolio of product candidates, which may require substantial financial resources and may ultimately be unsuccessful.

The longer term growth of our business depends upon our ability to expand the approved uses of octreotide capsules beyond acromegaly, if approved, and utilize our proprietary Transient Permeability Enhancer, or TPE, technology platform to potentially develop and commercialize other oral forms of therapies that are currently only available in injectable or other non-absorbable forms. In addition to the development and commercialization of octreotide capsules in acromegaly, if approved, we may pursue development of octreotide capsules for other indications or develop other product candidates alone or in collaboration with other parties. Because we eliminated substantially all of our research and discovery functions during the August 2016 reduction in workforce, we do not currently have the internal capacity to develop any new product candidates. We also may never be able to identify other peptide drugs or poorly absorbed small-molecule drugs that can successfully be developed into product candidates utilizing our TPE platform, let alone receive regulatory approval of such product candidates, and we may never be able to engage in licensing transactions that enable a third party to utilize TPE in the development of future product candidates.

Research programs to identify new disease targets and product candidates require substantial technical, financial and human resources whether or not we ultimately identify any product candidates, and we are not currently investing in such research programs. As a result, we may not be able to successfully identify any future product candidates or new indications for octreotide capsules.

There are a number of FDA, EMA and other health authority, as applicable, requirements that we must satisfy before we can commence a clinical trial. If we are able to identify additional potential product candidates, satisfaction of these regulatory requirements will entail substantial time, effort and financial resources. We may never satisfy these requirements. Any time, effort and financial resources we expend on development of other product candidates, which we do not currently contemplate, may impair our ability to continue development and commercialization of octreotide capsules for the treatment of acromegaly and other indications, if pursued, and we may never commence clinical trials of such development programs despite expending significant resources in pursuit of their development. If we do commence clinical trials of octreotide capsules in other indications besides acromegaly or other product candidates, these product candidates may never demonstrate sufficient safety and efficacy to be approved by the FDA or other regulatory authorities.

58

Table of Contents

Our ability to develop a viable pipeline of potential future products may require us to enter into acquisition, license or similar agreements with third parties, and we may not be successful in negotiating the necessary agreements, or in achieving economic terms that will be sufficiently favorable to justify development of one or more such future products.

As a result of the elimination of substantially all of our research functions, we are currently unable to develop future potential products through internal research programs. Therefore, we may consider expanding the scope of future potential product candidates by acquiring or licensing injectable or poorly absorbed drugs from third parties or licensing our TPE technology to third parties.

We may, however, be unable to license or acquire suitable product candidates from third parties for a number of reasons. In particular, the licensing and acquisition of pharmaceutical products is a competitive area. For example, several more established companies are also pursuing strategies to license or acquire products in the somatostatin analog field. These established companies may have a competitive advantage over us due to their size, cash resources and greater research, clinical development and commercialization capabilities. Other factors that may prevent us from licensing or otherwise acquiring suitable product candidates include the following:

- we may be unable to license or acquire the relevant product candidate or technology on terms that would allow us to make an appropriate return, or the financial terms required by the owners of those product candidates or technologies may be unfavorable enough to preclude successful development and commercialization for such products;
- companies that perceive us to be their competitors may be unwilling to assign or license their product rights to us;
- we do not currently have dedicated research, business development or commercial personnel on staff;
- we may be unable to identify suitable products or product candidates within our areas of expertise; or
- our receipt of the CRL could reduce third-party confidence in our TPE platform and potentially make us a less attractive partner.

In addition, even if we are able to successfully license or acquire suitable technology from third parties, there can be no assurance that we will be able to successfully develop product candidates from such technology or receive necessary approvals to commercialize any such product candidates.

We do not have sufficient human and financial resources to develop suitable potential product candidates through internal research programs, we may not have the resources to obtain rights from third parties, and we may not be able to license our TPE technology to third parties for development of future product candidates, thereby limiting our ability to develop a diverse product portfolio. If we are unable to develop such a portfolio, our business may suffer.

We may be unable to obtain orphan drug designation or exclusivity for future product candidates we may develop. If our competitors are able to obtain orphan drug exclusivity for their products that are the same as our product

candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Our octreotide capsules product candidate has been granted orphan designation in the United States and the European Union for the oral treatment of acromegaly. Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals diagnosed annually in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the European Commission, after reviewing the opinion of

Table of Contents

the EMA s Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the product candidate. Even if we request orphan drug designation for any future product candidates we may develop, there can be no assurances that the FDA or the European Commission will grant any of these product candidates such designation. Additionally, the designation by the FDA of any potential product candidates as an orphan drug does not guarantee that the FDA or the EMA will accelerate regulatory review of or ultimately approve that product candidate.

Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval of the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same drug and indication for that time period, except in limited circumstances. The applicable period is seven years in the United States and 10 years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even though we have obtained orphan drug designation for octreotide capsules in acromegaly and may obtain orphan drug designation for octreotide capsules in other indications or for future product candidates we may develop, we may not obtain orphan drug exclusivity and any such exclusivity that we do obtain may not effectively protect the product candidate from competition because different drugs can be approved for the same condition and the same drugs can be approved for different indications and might then be used off-label in our approved indication, if obtained. In the United States, even after an orphan drug is approved, the FDA can subsequently approve another drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In addition, if a potential future product candidate of ours receives an orphan drug designation and is approved for a particular indication or use within the rare disease or condition, the FDA may later approve the same drug for additional indications or uses within that rare disease or condition that are not protected by our exclusive approval. As a result, if our product is approved and receives orphan drug status, the FDA can still approve other drugs for use in treating the same indication or disease covered by our product, which could create a more competitive market for us.

Our 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 octreotide capsules and any future product candidates we may develop for which we obtain marketing approval. Our arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may affect the business or financial arrangements and relationships through which we would market, sell and distribute our products. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients rights are and will be applicable to our business. Restrictions under applicable federal and state healthcare laws and regulations that may affect our operations and expose us to areas of risk including the following:

the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in

Table of Contents

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 of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

federal civil and criminal false claims laws and civil monetary penalty laws, which impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, 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 criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services;

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

the ACA which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid or Children s Health Insurance Program to report annually to Centers for Medicare and Medicaid Services, or CMS, information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members; and

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

Efforts to ensure that our business arrangements with third parties are compliant with applicable healthcare laws and regulations will involve the expenditure of appropriate, and possibly significant, resources. Nonetheless, 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, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other healthcare providers or entities with whom

we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Legislative or regulatory reform of the health care system in the United States and foreign jurisdictions may adversely impact our business, operations or financial results.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. In particular, in March 2010, the ACA was signed into law. This legislation changes the current system of

Table of Contents

healthcare insurance and benefits intended to broaden coverage and control costs. The law also contains provisions that will affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following:

- mandatory rebates for drugs sold into the Medicaid program have been increased, and the rebate requirement has been extended to drugs used in risk-based Medicaid managed care plans;

- the definition of average manufacturer price was revised for reporting purposes, which could increase the amount of Medicaid drug rebates by state;

- the 340B Drug Pricing Program under the Public Health Service Act has been extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities;

- pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the donut hole ; and

- pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company s market share of prior year total sales of branded products to certain federal healthcare programs. If octreotide capsules or any of our future potential product candidates are approved, we expect our branded pharmaceutical sales to constitute a small portion of the total federal health program pharmaceutical market, and therefore would not expect this annual assessment to have a material impact on our financial condition.

Despite initiatives to invalidate the ACA, the U.S. Supreme Court has upheld certain key aspects of the legislation, including the requirement that all individuals maintain health insurance coverage or pay a penalty, referred to as the individual mandate, and a key provision of the ACA, which provides federal premium tax credits to individuals purchasing coverage through health insurance exchanges.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to repeal or replace elements of the ACA. Thus, the full impact of the ACA, or any law replacing elements of it, and the political uncertainty regarding any repeal and replacement on the ACA, on our business remains unclear.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending

reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013, which will remain in effect until 2025 unless additional congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

Table of Contents

In addition, in September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted giving the FDA enhanced post-marketing authority including the authority to require post-marketing studies and clinical trials, labeling changes based on new safety information and compliance with risk evaluations and mitigation strategies approved by the FDA. The FDA s exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to ensure compliance with post-approval regulatory requirements and potential restrictions on the sale and/or distribution of approved products. Other legislative and regulatory initiatives have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. For example, the Drug Supply Chain Security Act of 2013 imposes new obligations on manufacturers of certain pharmaceutical products related to product tracking and tracing. We do not know whether additional legislative changes will be enacted, or whether the FDA regulations, guidance documents or interpretations will be changed, or what the impact of such changes on the marketing approvals of octreotide capsules, if any, may be. In addition, increased scrutiny by Congress of the FDA s approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Further, in some foreign jurisdictions, including the European Union and Canada, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take 12 months or longer after the receipt of regulatory approval and product launch. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of octreotide capsules and any future product candidate we may develop to other available therapies. Our business could be harmed if reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels.

Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further, federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from octreotide capsules and any other product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

We may not be able to maintain our current product liability coverage, and, even if we do, our coverage may not be adequate to cover any or all liabilities that we may incur, which could decrease our cash and harm our business.

We currently have $10.0 million in product liability insurance coverage in the aggregate, which may not be adequate to cover any or all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. We intend to expand our product liability insurance coverage to include the sale of commercial products if we obtain marketing approval of octreotide capsules and any future product candidates we may develop, but we may be unable to obtain commercially reasonable product liability insurance. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us, particularly if judgments exceed our insurance coverage, could decrease our cash and harm our business. In addition, we may not be able to maintain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims, which could prevent or inhibit the commercial production and sale of our products.

Additionally, if any claims are brought against us, even if we are fully covered by insurance, we may suffer harm such as adverse publicity. We also could suffer diversion of attention of technical and management personnel and incur substantial costs in resolving disputes, including litigation, with our insurance provider regarding coverage.

63

Table of Contents

Risks Related to Our Reliance on Third Parties

We are, and expect to be for the foreseeable future, dependent on a limited number of third parties to manufacture octreotide capsules.

We do not currently have, nor do we plan to acquire, the capability or infrastructure to manufacture the API in octreotide capsules for use in our clinical trials or for commercial product, if regulatory approvals are obtained. We have qualified Novetide Ltd., a subsidiary of Teva Pharmaceuticals Industries Ltd., in Israel and an affiliate of Teva API, Inc., and Bachem Americas Inc. in the United States as our suppliers of the generic API, octreotide acetate. All excipients, or substances formulated together with the API that are used in the manufacture of octreotide capsules, are readily available. The octreotide API is lyophilized, formulated with our TPE technology, filled into capsules and enteric-coated by Lyophilization Services of New England Inc., or LSNE, in Bedford, NH and Capsugel, a division of Lonza, in Livingston, Scotland.

The facilities used by our contract manufacturers to manufacture octreotide capsules are evaluated by the FDA and other regulatory bodies. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMPs for manufacture of both API and finished drug products. These cGMP regulations cover all aspects of the manufacturing, testing, quality control and record keeping relating to octreotide capsules. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we will not be able to secure and/or maintain regulatory approval of our product candidate being manufactured at their manufacturing facilities. If the FDA or a comparable foreign regulatory authority finds deficiencies at these facilities, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval of or market octreotide capsules, if approved. For example, in its CRL, the FDA advised that, during a site inspection, certain deficiencies were conveyed to the representative of one of our suppliers that would need to be resolved before approval of our NDA for octreotide capsules. Although we were informed that the supplier received an EIR from the FDA, indicating that the FDA has concluded its inspection of the supplier and as of the date of its report considers outstanding deficiencies resolved, we expect that our suppliers will be subject to additional regulatory inspections in the future, including in connection with the FDA s review of any NDA we may submit in the future, if any, seeking approval of octreotide capsules in acromegaly. There can be no assurances that our suppliers will pass all future inspections, the failure of which could result in delays to our ability to receive regulatory approval for octreotide capsules.

Our contract manufacturers will be subject to ongoing periodic unannounced inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements. We do not have control over our contract manufacturers compliance with these regulations and requirements. Failure by any of our contract manufacturers to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure to grant approval to market octreotide capsules, delays, suspensions or withdrawals of approvals, operating restrictions and criminal prosecutions, any of which could harm our business. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. Failure by our contract manufacturers to comply with or maintain any of these requirements could impair our ability to develop, obtain regulatory approval of or market octreotide capsules.

If, for any reason, these third parties are unable or unwilling to perform, we may not be able to effectively terminate our agreements with them, and we may not be able to locate alternative manufacturers or formulators or enter into favorable agreements with them, and we cannot be certain that any such third parties will have the manufacturing capacity to meet future requirements. If these manufacturers or any alternate manufacturer of finished drug product experiences any significant difficulties in its respective manufacturing processes for our API or finished octreotide

capsules product or should cease doing business with us, we could experience significant interruptions in the supply of octreotide capsules or may not be able to create a supply of octreotide capsules at all. Were we to encounter manufacturing issues, our ability to produce a sufficient supply of octreotide capsules might be negatively affected. Our inability to coordinate the efforts of our third-party

Table of Contents

manufacturing partners, or the lack of capacity available at our third-party manufacturing partners, could impair our ability to supply octreotide capsules at required levels. Because of the significant regulatory requirements that we would need to satisfy in order to qualify a new bulk or finished product manufacturer, if we face these or other difficulties with our current manufacturing partners, we could experience significant interruptions in the supply of octreotide capsules if we decided to transfer the manufacture of octreotide capsules to one or more alternative manufacturers in an effort to deal with the difficulties.

Any manufacturing problem or the loss of a contract manufacturer could be disruptive to our operations and, if our products receive marketing approval, result in lost sales. Additionally, we rely on third parties to supply the raw materials needed to manufacture octreotide capsules. Any reliance on suppliers may involve several risks, including a potential inability to obtain critical materials and reduced control over production costs, delivery schedules, reliability and quality. Any unanticipated disruption to future contract manufacturers caused by problems at suppliers could delay shipment of octreotide capsules and, if approved for marketing, increase our cost of goods sold and result in lost sales.

We cannot guarantee that our current manufacturing and supply partners or any alternative service providers will be able to reduce the costs of commercial-scale manufacturing of octreotide capsules over time, particularly following the suspension of our commercial commitments to certain of our manufacturers following the receipt of the CRL. If the manufacturing costs of octreotide capsules remain at current levels or increase, these costs may significantly impact our future operating results. In order to reduce costs, we may need to develop and implement process improvements. However, in order to do so, we will need, from time to time, to notify or make submissions with regulatory authorities, and the improvements may be subject to approval by such regulatory authorities. We cannot be sure that we will receive these necessary approvals or that these approvals will be granted in a timely fashion. We also cannot guarantee that we will be able to enhance and optimize output in our commercial manufacturing process. If we cannot enhance and optimize output, we may not be able to reduce our costs over time.

We have previously established commercial manufacturing agreements with Teva API, Inc. for the API in octreotide capsules and with LSNE for certain testing and lyophilization services. Following our receipt of the CRL, we indefinitely suspended our commercial production commitments. In the future, if octreotide capsules are approved, we may not be able to reach or maintain agreements containing terms that are acceptable to us with our commercial manufacturers.

If our third-party manufacturers use hazardous and biological materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our development activities involve the controlled use of potentially hazardous substances, including chemical and biological materials by our third-party manufacturers. Our manufacturers are subject to federal, state and local laws and regulations in the United States governing medical, radioactive and hazardous materials. Although we believe that our manufacturers procedures for using, handling, storing and disposing of these materials comply with legally prescribed requirements, we cannot completely eliminate the risk of contamination or injury resulting from such materials. As a result of any such contamination or injury we may incur liability or local, city, state or federal authorities may curtail the use of these materials, interrupting our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our development and production efforts, which could harm our business, prospects, financial condition or results of operations.

65

Table of Contents

An important part of our strategy may be to enter into licensing or collaboration agreements with respect to octreotide capsules and future product candidates, if any, in certain territories. We may not be able to identify suitable collaborators and, even if we do, our dependence on such relationships may adversely affect our business.

Because we have limited resources, we may seek to enter into collaboration agreements with other pharmaceutical or biotechnology companies. Our strategy for commercializing octreotide capsules and any future product candidates we may develop may depend on our ability to enter into agreements with collaborators to obtain assistance and funding for the development and potential commercialization of our product candidates in the territories in which we may seek to partner. Despite our efforts, we may be unable to secure collaborative licensing or other arrangements that are necessary for us to further develop and commercialize our product candidates. Supporting diligence activities conducted by potential collaborators and negotiating the financial and other terms of a collaboration agreement are long and complex processes with uncertain results. Our receipt of the CRL from the FDA may cause potential collaborators to assign a lower probability to our regulatory success of octreotide capsules which could reduce the likelihood of our ability to enter into a collaboration on favorable terms, if at all. Even if we are successful in entering into one or more collaboration agreements, collaborations may involve greater uncertainty for us, as we have less control over certain aspects of our collaborative programs than we do over our proprietary development and commercialization programs.

Any failure by our partners to perform their obligations or any decision by our partners to terminate these agreements could negatively impact our ability to successfully develop, obtain regulatory approvals for and commercialize our product candidates. In the event we grant exclusive rights to such partners, we could be precluded from potential commercialization of our product candidate within the territories in which we have a partner. In addition, any termination of our collaboration agreements will terminate any funding we may receive under the relevant collaboration agreement and may impair our ability to fund further development efforts and our progress in our development programs. For example, in July 2014, Roche elected to terminate a license agreement with us for octreotide capsules. As a result, we assumed responsibility for the further development and commercialization of octreotide capsules and will receive no additional funding from Roche for this purpose.

Further, our potential future collaborators may develop alternative products or pursue alternative technologies either on their own or in collaboration with others, including our competitors, and the priorities or focus of our collaborators may shift such that our product candidates receive less attention or resources than we would like, or they may be terminated altogether. Any such actions by our potential future collaborators may harm our business prospects and ability to earn revenues. In addition, we could have disputes with our potential future collaborators, such as the interpretation of terms in our agreements. Any such disagreements could lead to delays in the development or commercialization of our product candidates or could result in time-consuming and expensive litigation or arbitration, which may not be resolved in our favor.

We rely, and will rely in the future, on third parties to conduct our clinical trials. If these third parties do not appropriately carry out their contractual duties, fail to conduct high-quality studies or meet expected deadlines, regulatory approval and commercialization of octreotide capsules or any future candidates we may develop could be delayed or not obtained at all.

We do not have the ability to conduct our clinical trials independently. We will continue to rely on third parties, including clinical investigators, third-party CROs and consultants, to monitor, manage data for, and execute our ongoing clinical programs for octreotide capsules, and we control only some aspects of their activities. Because we rely on third parties, our internal capacity to perform these functions is limited. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. Nevertheless, we are responsible for ensuring that each of our clinical trials are conducted in accordance with the

applicable protocol and legal, regulatory and scientific requirements and standards, including, for example, Good Laboratory Practices and Good Clinical Practices, or GCPs. Our reliance on third parties does not relieve us of our regulatory responsibilities. Regulatory authorities enforce GCPs through

Table of Contents

periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the relevant regulatory authorities may require us to perform additional clinical trials in support of our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. Failure to comply with these regulations may require us to repeat nonclinical studies and clinical trials, which would delay the regulatory approval process.

The third parties conducting our clinical trials are not our employees, and we cannot control whether or not they devote sufficient time and resources to our ongoing clinical programs. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval of or successfully commercialize octreotide capsules and any future product candidates we may develop. As a result, our results of operations and the commercial prospects for our product candidates could be harmed, our costs could increase and our ability to generate revenues could be delayed.

Risks Related to Our Financial Position and Capital Resources

We have incurred significant losses since our inception and anticipate that we will incur continued losses for the next several years and thus may never achieve or maintain profitability.

We have funded our operations to date primarily through proceeds from sales of our common stock, redeemable convertible preferred stock and, to a lesser extent, the issuance of convertible notes. On July 21, 2015, we completed the sale of 7,319,750 shares of our common stock in our initial public offering, or IPO, at a price to the public of $16.00 per share, resulting in net proceeds of approximately $106.5 million after deducting underwriting discounts and commissions and offering expenses payable by us. From our inception through December 31, 2016, we had received net proceeds of $267.9 million from such transactions, including amounts raised in the IPO. As of December 31, 2017, our cash, cash equivalents and marketable securities were $66.9 million. Since inception, we have incurred significant operating losses. Our net loss was $26.8 million and $61.1 million for the years ended December 31, 2017 and 2016, respectively. As of December 31, 2017, we had an accumulated deficit of $205.4 million.

We have no products approved for commercialization and have never generated any product revenue. We expect to incur operating losses for at least the next several years. Past operating losses, combined with expected future operating losses, have had and will continue to have an adverse effect on our cash resources, stockholders equity and working capital. In June 2016, in light of the CRL, we announced a corporate restructuring plan intended to focus our resources on the continued development of octreotide capsules and pursuit of regulatory approval in the United States and Europe for the maintenance treatment of adult acromegaly patients. This plan included a reduction of approximately 33% of our workforce in June 2016, including substantially all of our commercial personnel. In August 2016, we announced a second corporate restructuring plan which further reduced our workforce by approximately 44%, primarily in our research and administrative functions. In aggregate, these restructuring plans resulted in a reduction to our workforce of more than 60% since May 1, 2016. In November 2017, we finalized the termination of our lease agreement on our 24,000 square foot office facility in Waltham, MA which we no longer required following the 2016 workforce reductions. As a result, we recorded approximately $1.0 million of restructuring expenses during the year ended December 31, 2017. We expect to incur significant additional costs conducting and completing our CHIASMA OPTIMAL and MPOWERED clinical trials and to fund our operations in support of these clinical development activities. In addition, we will incur additional costs associated with operating as a public company. As a

result of these and other factors, we expect to continue to incur significant operating losses for the foreseeable future. Because of the numerous risks

Table of Contents

and uncertainties associated with developing and commercializing pharmaceutical products, we are unable to predict the extent of any future losses, when we will become profitable, if at all, or whether we will have the funds necessary to continue as a standalone business in the long term.

Even if we 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 could depress the value of our stock and impair our ability to raise capital, expand our business, maintain our development efforts, obtain regulatory approvals, diversify our product pipeline or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We have not generated revenue from any commercial products and may never be profitable.

Our ability to become profitable depends upon our ability to generate revenue. Unless and until marketing approval is obtained from either the FDA or EMA for octreotide capsules or any future product candidates we may develop, we may not be able to generate sufficient revenue to attain profitability. In addition, our ability to generate profits after any FDA or EMA approval of our product candidates is subject to our ability to contract for the manufacture of commercial quantities of our product candidates at acceptable cost levels and establish sales and marketing capabilities or identify and enter into one or more strategic collaborations to effectively market and sell any approved product candidate.

Even if octreotide capsules or any future product candidates are approved for commercial sale, any approved product candidate may not gain market acceptance or achieve commercial success. In addition, we would anticipate incurring significant costs associated with commercializing any approved product. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate product revenues, we will not become profitable and may be unable to continue operations without continued funding.

We have a limited operating history and no history of commercializing drugs, which may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Although we commenced operations in 2001, our operations to date have been largely focused on developing octreotide capsules, including undertaking nonclinical studies and conducting clinical trials. Octreotide capsules are our only current product candidate for which we have conducted clinical trials. We have completed only a single Phase 3 clinical trial to date with this product candidate, although we are currently conducting two Phase 3 clinical trials of octreotide capsules in acromegaly. We have not yet demonstrated our ability to successfully obtain regulatory approvals, manufacture a commercial-scale drug or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Consequently, any 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 drugs.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. If we are successful in obtaining marketing approval of octreotide capsules in acromegaly, we will need to transition at some point from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We will need additional capital to support our operations, which may be difficult to obtain and restrict our operations and would result in additional dilution to our stockholders.

Our business will require additional capital that we have not yet secured. In the short term, we expect to continue to conduct our second Phase 3 clinical trial of octreotide capsules to treat acromegaly MPOWERED required for European regulatory approval, and our third Phase 3 clinical trial of octreotide capsules to treat acromegaly CHIASMA OPTIMAL initiated in September 2017 to potentially secure approval in the United States for

Table of Contents

octreotide capsules. In June and August of 2016, following our receipt of the CRL and the End of Review meeting, we announced corporate restructuring plans intended to focus our resources on the continued development of octreotide capsules for the maintenance treatment of adult acromegaly patients.

The actual amount of funds that we will need will be determined by many factors, some of which are beyond our control, and we may need funds sooner than currently anticipated. These factors include but are not limited to:

- our efforts to obtain FDA approval of octreotide capsules in acromegaly, and to conduct a randomized, double-blinded and controlled Phase 3 clinical trial as the FDA strongly recommended in the CRL and that we are conducting under the CHIASMA OPTIMAL protocol agreed to in the SPA;
- the amount of our future operating losses;
- the timing of approvals, if any, of octreotide capsules in additional jurisdictions;
- the need and cost of conducting one or more additional clinical trials for octreotide capsules and any future drug candidates;
- the amount of our research and development, marketing, selling and general and administrative expenses;
- the extent to which we enter into, maintain, and derive revenues from licensing agreements, including potential agreements to out-license octreotide capsules, research and other collaborations, joint ventures and other business arrangements;
- our success in integrating product candidates, technologies or companies that we may acquire; and
- regulatory changes and technological developments in our markets.

General market conditions or the market price of our common stock may not support capital-raising transactions, such as an additional public or private offering of our common stock or other securities. In addition, our ability to raise additional capital may be dependent upon our stock being quoted on The NASDAQ Global Select Market or upon obtaining stockholder approval. There can be no assurance that we will be able to satisfy the criteria for continued listing on The NASDAQ Global Select Market or that we will be able to obtain stockholder approval if it is necessary. If we are unable to obtain additional funds on a timely basis or on terms favorable to us, we may be required to cease development of octreotide capsules, to sell some or all of our technology or assets or to merge all or a portion of our business with another entity. In the event additional financing is needed or advisable, we may seek to fund our operations through the sale of equity securities, additional debt financing and strategic collaboration agreements. We cannot be sure that additional financing from any of these sources will be available when needed or that, if available, the additional financing will be obtained on terms favorable to us or our stockholders. If we raise additional funds by selling shares of our capital stock, the ownership interest of our current stockholders will be diluted. If we attempt to

raise additional funds through strategic collaboration agreements, we may not be successful in obtaining collaboration agreements, or in receiving milestone or royalty payments under those agreements. The terms of any debt facility may involve significant cash payment obligations as well as covenants and specific financial ratios that may restrict our ability to develop and commercialize octreotide capsules or any future product candidates or operate our business. Any of these actions could raise substantial doubt about our ability to continue as a going concern and have a material adverse effect on our business, financial condition and results of operations.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights.

We may seek additional capital through a combination of private and public equity offerings, debt financings and collaboration, strategic and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing stockholders will be diluted, and

Table of Contents

the terms may include liquidation or other preferences that adversely affect the rights of our existing stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic alliance and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us.

Risks Related to Our Business and Industry

We depend on the knowledge and skill of our senior management and other key employees, and if we are unable to retain or if we fail to recruit additional highly skilled personnel, our business will be harmed.

Our ability to compete in the highly competitive pharmaceuticals industry depends in large part upon our ability to attract and retain highly qualified managerial and development personnel. As of March 1, 2018, we have a total of 16 full-time employees. In order to induce valuable employees to remain with us, we have provided employees with stock options that vest over time. The value to employees of stock options that vest over time is significantly affected by movements in our stock price that we cannot control and, together with our other compensation programs and benefits, may at any time be insufficient to counteract more lucrative offers from other companies.

We are highly dependent upon the principal members of our management team. These executives have significant research and development, regulatory, industry, operational, and/or corporate finance experience. Our receipt of a CRL from the FDA related to our NDA and expected octreotide capsules clinical development timelines may make the retention of these individuals, other principal members of our management team and key employees more challenging. The loss of any executive, other principal member of our management team, key employee or member of our board of directors could impair our ability to develop and commercialize octreotide capsules, if approved, and identify, develop and market new products and conduct successful operations.

In addition, if octreotide capsules are approved, we will likely need to hire a significant number of qualified technical, commercial, medical and administrative personnel. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. Other biopharmaceutical companies with which we compete for qualified personnel may have greater financial and other resources, different risk profiles, and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are unable to continue to attract and retain high-quality personnel, the rate and success at which we can develop and commercialize octreotide capsules, if approved, and any future product candidates we may develop would be impaired and could adversely affect our growth and financial performance.

We may acquire additional businesses or form strategic alliances in the future, and we may not realize the benefits of such acquisitions or alliances.

We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may have difficulty in developing, manufacturing and marketing the products of a newly acquired company that enhances the performance of our combined businesses or product lines to realize value from expected synergies. We cannot assure you that, following an acquisition, we will achieve the revenues or specific net income that justifies the acquisition.

70

Table of Contents

Potential technological changes in our field of business create considerable uncertainty.

We are engaged in the biopharmaceutical field, which is characterized by extensive research efforts and rapid technological progress. New developments in research are expected to continue at a rapid pace in both industry and academia. We cannot assure you that research and discoveries by others will not render octreotide capsules or future product candidates we may develop uncompetitive or obsolete. The longer-term success of our business depends upon our ability to develop octreotide capsules for other approved indications and utilize our TPE platform to develop and commercialize oral forms of therapies that are currently only available in injectable or other non-absorbable forms, which strategy assumes we first obtain regulatory approval of octreotide capsules in acromegaly. We cannot assure you that unforeseen problems will not develop with our TPE technology or applications thereof or that any commercially feasible products will ultimately be developed by us.

Our employees, independent contractors, consultants, commercial partners, principal investigators, CROs and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk that our employees, independent contractors, consultants, commercial partners, principal investigators, CROs and vendors may engage in fraudulent conduct or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, to provide accurate information to the FDA or comparable foreign regulatory authorities, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, and to report financial information or data accurately or disclose unauthorized activities to us. The misconduct of our employees and contractors could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. In connection with our IPO, we implemented a code of conduct and ethics for our directors, officers and employees, but it is not always possible to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Our business and operations would suffer in the event of computer system failures, cyber-attacks on our systems or deficiency in our cyber security.

Despite the implementation of security measures, our internal computer systems, and those of third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, malware, natural disasters, fire, terrorism, war and telecommunication, electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, our systems and those of our clinical service providers safeguard important confidential personal data regarding patients enrolled in our clinical trials. If a disruption event were to occur and cause interruptions in our operations, it could result in a disruption of our drug development programs. For example, the loss of clinical trial data from completed, ongoing or clinical trials that we may consider could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our

data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of octreotide capsules and any future product candidates we may develop could be delayed.

Table of Contents

Business disruptions could seriously harm our future revenues and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, military conflicts, acts of terrorism and other natural or man-made disasters or business interruptions. Some of our operations are in Israel, which has a history of certain conflicts. The occurrence of any business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce octreotide capsules. Our ability to obtain clinical supplies of octreotide capsules could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption, as we do not carry insurance to cover such risks.

Laws and regulations governing conduct of international operations may negatively impact our development, manufacture and sale of products outside of the United States and require us to develop and implement costly compliance programs.

As we have operations in Israel and may seek to further expand our operations outside of the United States, we must comply with numerous laws and regulations in Israel and each other jurisdiction in which we plan to operate. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where we must rely on third parties.

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring such companies to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the DOJ. The Securities and Exchange Commission, or SEC, is involved with enforcement of the books and records provisions of the FCPA.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain foreign nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. An expanding presence outside of the United States will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling octreotide capsules and any future product candidates we may develop outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term

disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure

Table of Contents

government contracts. Additionally, the SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA s accounting provisions.

Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.

We collect and store sensitive data, including intellectual property, our proprietary business information and that of our manufacturers, business partners, healthcare professionals and patients. This includes, where required or permitted by applicable laws, personally identifiable information. The secure maintenance of this information is critical to our operations and business strategy. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disrupt our operations, and damage our reputation which could adversely affect our business.

Compliance with changing European privacy laws could require us to incur significant costs or experience significant business disruption and failure to so comply could result in an adverse impact on our business.

In Europe, Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, or the Directive, has required European Union member states to implement data protection laws to meet the strict privacy requirements of the Directive. Among other requirements, the Directive regulates transfers of personally identifiable data that is subject to the Directive, or Personal Data, to countries such as the United States, that have not been found to provide adequate protection to such Personal Data. We have not in the past and cannot in the future rely upon adherence to the U.S. Department of Commerce s Safe Harbor Privacy Principles and compliance with the U.S.-EU and U.S.-Swiss Safe Harbor Frameworks as agreed to and set forth by the U.S. Department of Commerce, and the European Union and Switzerland, which established a means for legitimating the transfer of Personal Data by data controllers in the European Economic Area, or the EEA, to the United States. As a result of the October 6, 2015 European Union Court of Justice, or ECJ, opinion in Case C-362/14 (*Schrems v. Data Protection Commissioner*) regarding the adequacy of the U.S.-EU Safe Harbor Framework, the U.S. EU Safe Harbor Framework is no longer deemed to be a valid method of compliance with requirements set forth in the Directive (and member states implementations thereof) regarding the transfer of Personal Data outside of the EEA.

In February 2016, negotiators from Europe and the United States reached political agreement on a successor to the Safe Harbor framework that is being referred to as the EU-US Privacy Shield and a draft adequacy decision was presented by the European Commission on February 29, 2016. On April 13, 2016, the Article 29 Working Party, a body made up of a representative from the data protection authority of each EU member State, expressed strong concerns about the adequacy of the EU-US Privacy Shield. In its opinion on the draft adequacy decision, the Working Party noted that the framework does not incorporate some of the key principles of the EU data protection regime. Accordingly, the EU-US Privacy Shield was subject to further negotiations and revisions. On May 26, 2016, the European Parliament adopted a resolution and on July 8, 2016 the European Member States representatives approved the final version of the EU-US Privacy Shield, paving the way for the adoption of the decision by the European Commission. On July 12, 2016, the U.S. Department of Commerce announced that the EU-US Privacy Shield program would be open to registrants as of August 1, 2016. We conducted a self-assessment and subsequently self-certified under the Privacy Shield Framework in September 2016, and received a notice of acceptance of our self-certification in October 2016. However, there continue to be concerns about whether the EU-US Privacy Shield will face additional challenges (as the Safe Harbor framework did). We expect that for the immediate future, we will

continue to face uncertainty as to whether our efforts to comply with our obligations under European privacy laws will be sufficient. If we are investigated by a European data protection authority, we may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on our existing

Table of Contents

business. We may find it necessary to establish systems to maintain personal data originating from the EU in the EEA, which may involve substantial expense and may cause us to need to divert resources from other aspects of our business, all of which may adversely affect our business.

The Directive will be replaced with the European General Data Protection Regulation, which will enter into force on May 25, 2018, and which will impose additional obligations and risk upon our business and which will increase substantially the penalties to which we could be subject in the event of any non-compliance, including fines of up to 10,000,000 Euros or up to 2% of the total worldwide annual turnover for certain comparatively minor offenses, or up to 20,000,000 Euros or up to 4% of the total worldwide annual turnover for more serious offenses. We may incur substantial expense in complying with the new obligations to be imposed by the European General Data Protection Regulation and we may be required to make significant changes in our business operations, all of which may adversely affect our revenues and our business overall. Given the breadth and depth of changes in data protection obligations, preparing to meet the GDPR s requirements before its application on May 25, 2018 requires time, resources and a review of the technology and systems currently in use against the GDPR s requirements.

Exchange rate fluctuations between the U.S. dollar and non-U.S. currencies may negatively affect our results of operations.

The U.S. dollar is our functional and reporting currency; however, a portion of our operations are currently conducted in Israel and most of the Israeli expenses are currently paid in New Israeli Shekels, or NIS. We also contract with CROs internationally, primarily for the execution of clinical trials and manufacturing activities. A portion of these transactions are settled in Euros or Great British Pounds, or GBPs. As a result, we are exposed to the risk that the NIS, Euro or GBP may appreciate relative to the U.S. dollar, or, if the NIS, Euro or GBP instead devalue relative to the U.S. dollar, that the relative inflation rate may exceed such rate of devaluation, or that the timing of such devaluation may lag behind the relative inflation. In any such event, the U.S. dollar cost of our operations in Israel and transactions with certain CROs would increase and our U.S. dollar-denominated results of operations would be adversely affected. To date, we have not engaged in hedging transactions. In the future, we may enter into currency hedging transactions to decrease the risk of financial exposure from fluctuations in the exchange rates of our principal operating currencies. These measures, however, may not adequately protect us from the material adverse effects of such fluctuations. If the U.S. dollar cost of our operations increases, our U.S. dollar-measured results of operations will be adversely affected. See Management s Discussion and Analysis of Financial Condition and Results of Operations Quantitative and Qualitative Disclosure About Market Risk.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property rights or if our intellectual property rights are inadequate to protect our technology and product candidates, our competitors could develop and commercialize technology and drugs similar to ours, and our competitive position could be harmed.

Our commercial success will depend in large part on our ability to obtain and maintain patent and other intellectual property protection in the United States and other countries with respect to our proprietary technology and products. We rely on trade secret, patent, copyright and trademark laws, and confidentiality and other agreements with employees and third parties, all of which offer only limited protection. Our strategy is to seek patent protection for our product candidates and compositions, their methods of use and processes for their manufacture, and any other aspects of inventions that are commercially important to the development of our business.

The patent prosecution process is expensive and time-consuming, and we and any future licensors and licensees may not be able to apply for or prosecute patents on certain aspects of our product candidates or delivery technologies at a

reasonable cost, in a timely fashion, or at all. We may not have the right to control the

Table of Contents

preparation, filing and prosecution of patent applications, or to maintain the rights to patents licensed to third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is also possible that we or any future licensors or licensees, will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, our patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If any future licensors or licensees, are not fully cooperative or disagree with us as to the prosecution, maintenance, or enforcement of any patent rights, such patent rights could be compromised and we might not be able to prevent third parties from making, using, and selling competing products. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid or unenforceable. Moreover, our competitors may independently develop equivalent knowledge, methods, and know-how. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business, financial condition, and operating results.

The patent positions of biotechnology and pharmaceutical companies generally are highly uncertain, involve complex legal and factual questions and have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of any patents that issue, are highly uncertain. The steps we have taken to protect our proprietary rights may not be adequate to preclude misappropriation of our proprietary information or infringement of our intellectual property rights, both inside and outside the United States. Further, the examination process may require us to narrow the claims of pending patent applications, which may limit the scope of patent protection that may be obtained if these applications issue. The rights that may be granted under future issued patents may not provide us with the proprietary protection or competitive advantages we are seeking. If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection obtained is not sufficient, our competitors could develop and commercialize technology and products similar or superior to ours, and our ability to successfully commercialize our technology and products may be impaired.

With respect to patent rights, we do not know whether any of our patent applications will result in issued patents or, if any of our patent applications do issue, whether such patents will protect our technology and drugs, in whole or in part, or whether such patents will effectively prevent others from commercializing competitive technologies and products. There is no guarantee that any of our issued or granted patents will not later be found invalid or unenforceable. 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, until they are issued as a patent. Therefore, we cannot be certain that we were the first to make the inventions claimed in our pending patent applications, that we were the first to file for patent protection of such inventions, or that we have found all of the potentially relevant prior art relating to our patents and patent applications that could invalidate one or more of our patents or prevent one or more of our patent applications from issuing. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may initiate oppositions, interferences, re-examinations, post-grant reviews, *inter partes* reviews, nullification or derivation actions in court or before patent offices or similar proceedings challenging the validity, enforceability, or scope of such patents, which may result in the patent claims being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates, or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties.

Furthermore, 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. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or

held unenforceable, in whole or in part, which could limit our ability to stop others from

Table of Contents

using or commercializing similar or identical technology and drugs, or limit the duration of the patent protection of our technology and drugs. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In a patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. A court may decide that a patent of ours or our licensors is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. With respect to the validity question, for example, we cannot be certain that no invalidating prior art exists. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, found unenforceable, or interpreted narrowly, and it could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on one or more of our products or certain aspects of our platform technology. Such a loss of patent protection could have an adverse impact on our business.

Interference proceedings brought by the USPTO may be necessary to determine the priority of inventions with respect to our patents and patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if a prevailing party does not offer us a license on terms that are acceptable to us. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distraction of our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our proprietary rights, particularly in countries where the laws may not protect those rights as fully as in the United States. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Moreover, we may be subject to a third-party pre-issuance submission of prior art to the USPTO or other foreign patent offices, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings 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 drugs and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop, or commercialize current or future product candidates.

76

Table of Contents

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

Filing, prosecuting and defending patents on polypeptide containing capsules including octreotide capsules and our TPE platform throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States may be less extensive than those in the United States. In addition, the laws and practices of some foreign countries do not protect intellectual property rights, especially those relating to life sciences, to the same extent as federal and state laws in the United States. For example, novel formulations of existing drugs and manufacturing processes may not be patentable in certain jurisdictions, and the requirements for patentability may differ in certain countries, particularly developing countries. Also, some foreign countries, including European Union countries, India, Japan and China, have compulsory licensing laws under which a patent owner may be compelled under certain circumstances to grant licenses to third parties. Consequently, we may have limited remedies if patents are infringed or if we are compelled to grant a license to a third party, and we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions into or within the United States or other jurisdictions. This could limit our potential revenue opportunities. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products, and may export otherwise infringing products to territories where we have patent protection, but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from competing with us in these jurisdictions. Accordingly, our efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from our intellectual property. We may not prevail in any lawsuits that we initiate in these foreign countries and the damages or other remedies awarded, if any, may not be commercially meaningful.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which could be uncertain and could harm our business.

While our product candidate is in clinical trials, we believe that the use of our product candidate in these clinical trials falls within the scope of the exemptions provided by 35 U.S.C. Section 271(e) in the United States, which exempts from patent infringement liability activities reasonably related to the development and submission of information to the FDA. As our current and any future product candidates progress toward commercialization, the possibility of a patent infringement claim against us increases. There can be no assurance that our current and any future product candidates do not infringe other parties patents or other proprietary rights, however, and competitors or other parties may assert that we infringe their proprietary rights in any event. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates, including interference or derivation proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we are found to infringe a third

party s intellectual property rights, we could be required to obtain a license from such third party to continue commercializing our product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if a license can be obtained on

Table of Contents

acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. If we fail to obtain a required license, we may be unable to effectively market product candidates based on our technology, which could limit our ability to generate revenue or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Alternatively, we may need to redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. Under certain circumstances, we could be forced, including by court order, to cease commercializing our product candidates. In addition, in any such proceeding or litigation, we could be found liable for substantial monetary damages, potentially including treble damages and attorneys fees, if we are found to have willfully infringed. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets could have a similar negative impact on our business.

The cost to us in defending or initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management s attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our development efforts and limit our ability to continue our operations.

Octreotide capsules or any future products we may develop may infringe the intellectual property rights of others, which could increase our costs and delay or prevent our development and commercialization efforts.

Our success depends in part on avoiding infringement of the proprietary technologies of others. The pharmaceutical industry has been characterized by frequent litigation regarding patent and other intellectual property rights. Identification of third-party patent rights that may be relevant to our proprietary technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. Additionally, because patent applications are maintained in secrecy until the application is published, we may be unaware of third-party patents that may be infringed by commercialization of octreotide capsules or any future product candidate. There may be certain issued patents and patent applications claiming subject matter that we may be required to license in order to research, develop, or commercialize octreotide capsules, and we do not know if such patents and patent applications would be available to license on commercially reasonable terms, or at all. Any claims of patent infringement asserted by third parties would be time-consuming and may:

result in costly litigation;

divert the time and attention of our technical personnel and management;

cause product development or commercialization delays;

prevent us from commercializing a product until the asserted patent expires or is held finally invalid or not infringed in a court of law;

require us to cease or modify our use of the technology and/or develop non-infringing technology; or

require us to enter into royalty or licensing agreements.

Although no third party has asserted a claim of infringement against us, others may hold proprietary rights that could prevent octreotide capsules or any future product candidates from being marketed. Any patent-related legal action against our collaborators or us claiming damages and seeking to enjoin commercial activities relating to octreotide capsules or our processes could subject us to potential liability for damages and require us to obtain a license to continue to manufacture or market octreotide capsules or any future product candidates. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. In addition, we cannot be sure that we could

Table of Contents

redesign octreotide capsules or any future product candidates or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing octreotide capsules or a future product candidate, which could harm our business, financial condition and operating results.

A number of companies, including several major pharmaceutical companies, have conducted research on pharmaceutical uses of somatostatin analogs, which resulted in the filing of many patent applications related to this research. If we were to challenge the validity of these or any issued U.S. patent in court, we would need to overcome a statutory presumption of validity that attaches to every U.S. patent. This means that, in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent s claims. If we were to challenge the validity of these or any issued U.S. patent in an administrative trial before the Patent Trial and Appeal Board in the USPTO, we would have to prove that the claims are unpatentable by a preponderance of the evidence. There is no assurance that a jury and/or court would find in our favor on questions of infringement, validity or enforceability.

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 seek to market generic versions of any approved products by submitting abbreviated NDAs to the FDA in which our competitors claim that our patents are invalid, unenforceable or not infringed. Alternatively, our competitors may seek approval to market their own products that are the same as, similar to or otherwise competitive with octreotide capsules and any future product candidates we may develop. In these circumstances, we may need to defend or assert our patents, by means including filing lawsuits alleging patent infringement requiring us to engage in complex, lengthy and costly litigation or other proceedings. In any of these types of proceedings, a court or government agency with jurisdiction may find our patents invalid, unenforceable or not infringed. We may also fail to identify patentable aspects of our development activities before it is too late to obtain patent protection. 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.

Changes in either U.S. or foreign patent law or interpretation of such laws could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and it therefore is costly, time-consuming and inherently uncertain. In addition, on September 16, 2011, the Leahy-Smith America Invents Act, or the AIA, was signed into law. The AIA includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a first-to-file system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard

necessary to invalidate a patent claim in USPTO proceedings compared to the evidentiary standard in United States federal court, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to

Table of Contents

invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

Depending on decisions by the United States Congress, the federal courts, the USPTO, or similar authorities in foreign jurisdictions, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patent protection for certain aspects of our product candidates and delivery technologies, we also consider trade secrets, including confidential and unpatented know-how important to the maintenance of our competitive position. We protect trade secrets and confidential and unpatented know-how, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants that obligate them to maintain confidentiality and assign their inventions to us. Despite these efforts, any of these parties may breach the agreements 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, some courts in the United States and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them 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 competitive position would be harmed.

If our trademarks are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our trademarks may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. If we are unable to establish name recognition based on our trademarks, we may not be able to compete effectively and our business may be adversely affected.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other companies and universities. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

Risks Related to Our Operations in Israel

The tax benefits available to us under Israeli law require us to meet several conditions and may be terminated or reduced in the future, which would increase our costs and taxes.

We are able to take advantage of tax exemptions and reductions resulting from the beneficiary enterprise status of our facilities in Israel. To remain eligible for these tax benefits, we must continue to meet certain conditions

Table of Contents

stipulated in the Israeli Law for the Encouragement of Capital Investments, 1959 and its regulations. If we fail to meet these conditions in the future, the tax benefits would be canceled and we could be required to refund any tax benefits we might already have received. These tax benefits may not be continued in the future at their current levels or at any level. In recent years, the Israeli government has reduced the benefits available and has indicated that it may further reduce or eliminate some of these benefits in the future. The termination or reduction of these tax benefits may increase our income taxes in the future. Additionally, if we increase our activities outside of Israel, for example, by future acquisitions, our increased activities generally will not be eligible for inclusion in Israeli tax benefit programs. Our move out of our Jerusalem location in 2016 may also negatively impact the local tax benefits we have received by operating there.

We may become subject to claims for remuneration or royalties for assigned service invention rights by our employees, which could result in litigation and harm our business.

A significant portion of our intellectual property has been developed by our employees in the course of their employment for us. Under the Israeli Patent Law, 5727-1967 (the Patent Law), and recent decisions by the Israeli Supreme Court and the Israeli Compensation and Royalties Committee, a body constituted under the Patent Law, employees may be entitled to remuneration for intellectual property that they develop for us unless they waive any such rights. Although we enter into agreements with our employees pursuant to which they agree that any inventions created in the scope of their employment or engagement are owned exclusively by us, and our current separation agreements with Israeli employees who have left our company include a waiver of all claims, rights or payments under Israeli law, we may still face claims demanding remuneration. As a consequence of such claims, we could be required to pay additional remuneration or royalties to our current and former employees, or be forced to litigate such claims, which could negatively affect our business.

Our development and administrative facilities and one of our third-party manufacturers are located in Israel and, therefore, our business could be hurt by political and military instability affecting Israel.

Our development and administrative facilities and one of our third-party manufacturers facilities are located in Israel. Accordingly, political, economic and military conditions in Israel and the surrounding region may directly affect our business. Any hostilities involving Israel or the interruption or curtailment of trade within Israel or between Israel and its trading partners could materially and adversely affect our business, financial condition and results of operations and could make it more difficult for us to raise capital. Instability in the region may lead to deterioration of the political relationships that exist between Israel and these countries and has raised concerns regarding security in the region and the potential for armed conflict. Our commercial insurance does not cover losses that may occur as a result of an event associated with the security situation in the Middle East. Any losses or damages incurred by us could have an adverse effect on our business. Any armed conflicts, terrorist activities or political instability in the region could materially and adversely affect our business, financial condition and results of operations.

Our operations may be disrupted as a result of the obligation of Israeli citizens to perform military service.

Many Israeli citizens are obligated to perform several days, and in some cases more, of annual military reserve duty each year until they reach the age of 40 (or older, for reservists who are military officers or have certain occupations) and, in the event of a military conflict, may be called to active duty. In response to increases in terrorist activity, there have been periods of significant call-ups of military reservists. It is possible that there will be military reserve duty call-ups in the future. Our operations could be disrupted by such call-ups, which may include the call-up of members of our management. Such disruption could harm our business, financial condition and results of operations.

81

Table of Contents

Under current Israeli law, we may not be able to enforce our Israeli employees covenants not to compete and therefore may be unable to prevent our competitors from benefiting from the expertise of some of our former employees.

We generally enter into non-competition agreements with our key employees, in most cases within the framework of their employment agreements. These agreements prohibit our key employees, if they cease working for us, from competing directly with us or working for our competitors for a limited period. Under applicable Israeli law, it is difficult (and may even be impossible) to enforce these agreements or any part thereof against our Israeli employees unless it can be shown that there are special circumstances in any particular case. If we cannot enforce our non-competition agreements against our Israeli employees, then we may be unable to prevent our competitors from benefiting from the expertise of these former employees, which could impair our business, results of operations and ability to capitalize on our proprietary information.

Risks Related to Our Common Stock

We may not be able to utilize a significant portion of our net operating loss carryforwards, which could negatively impact our profitability.

At December 31, 2017, we had federal net operating loss, or NOL, carryforwards of approximately $146.4 million. The federal NOL carryforwards expire at various dates through 2037. At December 31, 2017, there were no NOL carryforwards in our Israeli subsidiary.

Under Section 382 of the Internal Revenue Code of 1986, as amended, or Section 382, substantial changes in our ownership may limit the amount of federal NOL carryforwards that can be utilized annually in the future to offset our U.S. federal taxable income. Specifically, this limitation may arise in the event of a cumulative change in our ownership of more than 50% within any three-year period. Management has determined that we experienced an ownership change for purposes of Section 382 on August 16, 2005 and May 12, 2008. These ownership changes resulted in annual limitations to the amount of NOL carryforwards that can be utilized to offset future taxable income, if any, at the federal level. The annual limit is approximately $0.1 million for 2017 and each year thereafter. These annual limitations resulted in the loss of our ability to utilize approximately $8.9 million in federal NOL carryforwards, which resulted in a write-off of approximately $3.0 million of federal deferred tax assets prior to 2014. In addition, changes in our stock ownership, which are outside of our control, may have triggered an additional ownership change, as may future changes in our stock ownership. If additional ownership changes have occurred or occur in the future, our ability to utilize our net operating losses to offset income if we attain profitability may be substantially limited.

Our directors, executive officers and principal stockholders exercise significant control over our company, which will limit your ability to influence corporate matters.

As of December 31, 2017, our executive officers, directors and principal stockholders collectively controlled approximately 62.4% of our outstanding common stock, excluding any shares of common stock that such persons may have the right to acquire upon exercise of outstanding options or warrants. As a result, these stockholders, if they act together, will be able to influence our management and affairs and all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions.

Provisions of Delaware law or our charter documents could delay or prevent an acquisition of our company, even if the acquisition would be beneficial to our stockholders, and could make it more difficult for you to change our current management.

Provisions of Delaware law and our amended and restated certificate of incorporation and amended and restated bylaws, may discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their

Table of Contents

shares. These provisions may also prevent or delay attempts by stockholders to replace or remove our current management or members of our board of directors. These provisions include:

- a classified board of directors;
- limitations on the removal of directors;
- advance notice requirements for stockholder proposals and nominations;
- the inability of stockholders to act by written consent or to call special meetings;
- the ability of our board of directors to make, alter or repeal our amended and restated bylaws; and
- the authority of our board of directors to issue preferred stock with such terms as our board of directors may determine.

The affirmative vote of the holders of at least 75% of our shares of capital stock entitled to vote, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class, is necessary to amend or repeal the above provisions that are contained in our amended and restated certificate of incorporation. In addition, absent approval of our board of directors, our amended and restated bylaws may only be amended or repealed by the affirmative vote of the holders of at least 75% of our shares of capital stock entitled to vote.

In addition, we are subject to the provisions of Section 203 of the Delaware General Corporation Law, which limits business combination transactions with stockholders of 15% or more of our outstanding voting stock that our board of directors has not approved. These provisions and other similar provisions make it more difficult for stockholders or potential acquirers to acquire us without negotiation. These provisions may apply even if some stockholders may consider the transaction beneficial to them.

As a result, these provisions could limit the price that investors are willing to pay in the future for shares of our common stock. These provisions might also discourage a potential acquisition proposal or tender offer, even if the acquisition proposal or tender offer is at a premium over the then current market price for our common stock.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim for breach of a fiduciary duty owed by any of our directors, officers or other employee to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws

or (iv) any action asserting a claim governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation and amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions.

The trading price of our common stock may be volatile, and your investment in our common stock could decline in value and incur substantial losses.

On July 21, 2015, we completed the sale of 7,319,750 shares of our common stock in our IPO, at a price to the public of $16.00 per share. Since shares of our common stock were sold in our IPO, our stock price has reached a

Table of Contents

high of $30.52 per share and a low of $1.25 per share through March 1, 2018. There has been a public market for our common stock for only a relatively short period of time. Although our common stock is listed on The NASDAQ Global Select Market, an active public market for our common stock may not emerge or be sustained.

In addition, the market price for our common stock may fluctuate significantly in response to a number of factors, including:

- our interactions with the FDA regarding our product candidate, octreotide capsules in acromegaly;
- the enrollment and results of our MPOWERED and CHIASMA OPTIMAL Phase 3 clinical trials of octreotide capsules or any future clinical trials we may conduct, or changes in the development status of octreotide capsules or any other product candidates we may develop;
- any delay in our regulatory filings for octreotide capsules or any other future product candidate and any adverse development or perceived adverse development with respect to the applicable regulatory authority s review of such filings;
- adverse results or delays in clinical trials;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval of octreotide capsules, such as occurred on April 15, 2016 with the FDA s CRL to our NDA;
- changes in laws or regulations applicable to octreotide capsules or any other future product candidates, including clinical trial requirements for approvals;
- adverse developments concerning our manufacturers;
- our inability to obtain adequate supply of clinical trial material or for any approved drug or inability to do so at acceptable prices;
- our inability to establish collaborations, if needed;
- failure to commercialize octreotide capsules or any other future product candidates, if approved;

our ability to obtain coverage and adequate reimbursement from third-party payors for octreotide capsules or any other future product candidates, if approved;

unanticipated serious safety concerns related to the use of octreotide capsules or any other future product candidates;

our ability to effectively manage our operations or changes in organizational structure;

the size and growth of our initial target markets;

actual or anticipated variations in our operating results;

changes in financial estimates by us or by any securities analysts who might cover our stock;

conditions or trends in our industry;

changes in the market valuations of similar companies;

stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry;

publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;

announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;

Table of Contents

announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;

capital commitments;

investors general perception of our company and our business;

recruitment or departure of key personnel;

sales of our common stock in the future, including sales by our directors and officers or specific stockholders;

overall performance of the equity markets;

trading volume of our common stock;

changes in accounting practices;

ineffectiveness of our internal controls;

disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;

significant lawsuits, including patent or stockholder litigation, and developments related thereto;

general political and economic conditions; and

other events or factors, many of which are beyond our control.

We are the subject of securities litigation, which is expensive and may divert our management s attention.

On June 9, 2016, Chiasma, Inc. and certain of our current and former officers were named as defendants in a purported federal securities class action lawsuit filed in the United States District Court for the District of Massachusetts, styled *Gerneth v. Chiasma, Inc., et al*. This lawsuit challenges our public statements regarding our Phase 3 clinical trial methodology for octreotide capsules and our ability to obtain FDA approval for the marketing and sale of octreotide capsules. In December 2016, a lead plaintiff was appointed in the case. An amended complaint was filed by the lead plaintiff on February 10, 2017 similarly challenging our statements regarding the Phase 3 clinical trial methodology and results, and our ability to obtain FDA approval for octreotide capsules, in violation of Sections

11 and 15 of the Securities Act of 1933. The amended complaint adds as defendants current and former members of our board of directors, as well as the investment banks that underwrote our IPO on July 15, 2015. The lead plaintiff seeks to represent a class of all purchasers of our stock in our IPO. The plaintiff is seeking an unspecified amount of compensatory damages on behalf of himself and members of a putative shareholder class, including interest and reasonable costs and expenses incurred in litigating the action, and any other relief the court determines is appropriate. The defendants filed a motion to dismiss the amended complaint on March 27, 2017 and on February 15, 2018, the court denied defendants motion to dismiss. We believe this lawsuit is meritless and intend to vigorously defend against it. At this time, no assessment can be made as to the likely outcome of this lawsuit or whether the outcome will be material to us.

This litigation and any matters arising out of the allegations may result in substantial costs and divert our management s attention from other business concerns, which could seriously harm our business. We may not be successful in defending these claims and cannot provide assurance that insurance proceeds will be sufficient to cover any costs or liability under such claims.

We are an emerging growth company and we intend to take advantage of reduced disclosure and governance requirements applicable to emerging growth companies, which could result in our securities being less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we intend to take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not

Table of Contents

emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years following the year of our IPO, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700 million as of June 30 in any year before that time or if we have total annual gross revenue of $1.1 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our securities less attractive as a result, there may be a less active trading market for our securities and the price of our securities may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. As a result, changes in U.S. generally accepted accounting principles or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could adversely affect our financial position and results of operations.

We have never paid cash dividends on our capital stock and we do not anticipate paying any dividends in the foreseeable future. Consequently, any gains from an investment in our common stock will likely depend on whether the price of our common stock increases, which may not occur.

We have not paid cash dividends on any of our classes of capital stock to date and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Consequently, in the foreseeable future, you will likely only experience a gain from your investment in our common stock if the price of our common stock increases.

We incur significant increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives and other activities associated with being a public company.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, as well as rules subsequently implemented by the SEC and The NASDAQ Stock Market, has imposed various new requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Our management and other personnel are required to devote a substantial amount of time to these new compliance initiatives. Moreover, these rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time consuming and costly. These rules and regulations may make it more difficult and more expensive for us to maintain our existing director and officer liability insurance or to obtain similar coverage from an alternative provider.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, pursuant to Section 404 of the Sarbanes-Oxley

Table of Contents

Act, we are required to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting. Our testing, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 will require us to continue to incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we may need to hire additional accounting and financial staff. Moreover, if we are not able to comply with the requirements of Section 404 in a timely manner or if we or our independent registered public accounting firm identifies deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by The NASDAQ Stock Market, the SEC or other regulatory authorities, which would require additional financial and management resources.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, the Sarbanes-Oxley Act and the rules and regulations of the stock market on which our common stock is listed. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. We must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting as required by Section 404 of the Sarbanes-Oxley Act. This requires that we incur substantial additional professional fees and that we expend significant management efforts. Prior to our IPO, we had never been required to test our internal control within a specified period, and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

We may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system s objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our stock could decline and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the SEC or other regulatory authorities.

In addition, if, as a result of restructuring the company, we increase our reliance on contractors for important business functions, it may be more difficult to collect, analyze and report the information we are obligated to disclose as a public company and this could result in a material misstatement or omission in our disclosures.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is otherwise doing well.

If our existing stockholders sell, or indicate an intent to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline significantly. As of December 31, 2017, we had

24,381,605 outstanding shares of common stock, assuming no exercise of outstanding options or warrants.

In addition, the 3,609,766 shares subject to outstanding options under our stock option plans, the 3,190,015 shares reserved for future issuance under our stock option plans and the 3,567,015 shares subject to outstanding warrants will become eligible for sale in the public market in the future, subject to certain legal and contractual

Table of Contents

limitations. Moreover, holders of approximately 16,543,995 shares of our common stock have the right to require us to register these shares under the Securities Act pursuant to an investors rights agreement. If our existing stockholders sell substantial amounts of our common stock in the public market, or if the public perceives that such sales could occur, this could have an adverse impact on the market price of our common stock, even if there is no relationship between such sales and the performance of our business.

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

The trading market for our securities will depend in part on the research and reports that securities or industry analysts publish about us or our business. Since our IPO, four securities analysts have initiated coverage on our company. Since these coverage initiations, and following the receipt of the CRL to our NDA from the FDA, each of these analysts has downgraded their ratings on and lowered their price targets for our stock, three have since dropped coverage, and the fourth has not written an update on us since January 2017. In the event that one or more analysts who now, or in the future, cover us further downgrades our stock or publishes inaccurate or unfavorable research about our business, our trading price would likely decline. If one or more analysts, now or in the future, cease coverage of our company or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our trading price and trading volume to decline.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters, where our principal executive and administration functions are primarily located in a subleased facility in Waltham, Massachusetts. Our Waltham sublease expires in November 2020. In addition, our international operations are headquartered in a leased facility located in Ness Ziona, Israel, where our development and supply chain operational functions are primarily based. Our Ness Ziona lease expires in December 2020. Based on our current operating plans, we believe our current facilities are adequate.

Item 3. Legal Proceedings

On June 9, 2016, Chiasma, Inc. and certain of our current and former officers were named as defendants in a purported federal securities class action lawsuit filed in the United States District Court for the District of Massachusetts, styled *Gerneth v. Chiasma, Inc., et al*. This lawsuit challenges our public statements regarding our Phase 3 clinical trial methodology for octreotide capsules and our ability to obtain FDA approval for the marketing and sale of octreotide capsules. In December 2016, a lead plaintiff was appointed in the case. An amended complaint was filed by the lead plaintiff on February 10, 2017 similarly challenging our statements regarding the Phase 3 clinical trial methodology and results, and our ability to obtain FDA approval for octreotide capsules, in violation of Sections 11 and 15 of the Securities Act of 1933. The amended complaint adds as defendants current and former members of our board of directors, as well as the investment banks that underwrote our initial public offering (IPO) on July 15, 2015. The lead plaintiff seeks to represent a class of all purchasers of our stock in our IPO. The plaintiff is seeking an unspecified amount of compensatory damages on behalf of himself and members of a putative shareholder class, including interest and reasonable costs and expenses incurred in litigating the action, and any other relief the court

determines is appropriate. The defendants filed a motion to dismiss the amended complaint on March 27, 2017 and on February 15, 2018, the court denied defendants motion to dismiss. We believe this lawsuit is meritless and intend to vigorously defend against it. At this time, no assessment can be made as to the likely outcome of this lawsuit or whether the outcome will be material to us.

Table of Contents

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Market for Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock began trading on The NASDAQ Global Market under the symbol CHMA on July 16, 2015. The following table sets forth the high and low sales prices of our common stock as reported on The NASDAQ Global Market for the years ended December 31, 2017 and 2016:

	High	Low
Year ended December 31, 2017		
First quarter ended March 31, 2017	$ 2.30	$ 1.55
Second quarter ended June 30, 2017	$ 1.85	$ 1.25
Third quarter ended September 30, 2017	$ 2.65	$ 1.25
Fourth quarter ended December 31, 2017	$ 2.95	$ 1.55
Year ended December 31, 2016		
First quarter ended March 31, 2016	$ 19.71	$ 7.75
Second quarter ended June 30, 2016	$ 13.38	$ 2.50
Third quarter ended September 30, 2016	$ 3.19	$ 2.40
Fourth quarter ended December 31, 2016	$ 3.71	$ 1.75

Holders of Record

On March 8, 2018, the closing price per share of our common stock was $1.60 as reported on the NASDAQ Global Market, and we had approximately 22 stockholders of record. In addition, we believe that a significant number of beneficial owners of our common stock hold their shares in street name.

Dividend Policy

We have never declared or paid cash dividends on our capital stock and do not anticipate paying any dividends in the foreseeable future. We intend to retain future earnings, if any, to operate and expand the business. Payment of any future dividends would be at the discretion of our Board of Directors after taking into account various factors, including our financial condition, operating results, cash needs and growth plans.

Table of Contents

Stock Price Performance Graph

Set forth below is a graph comparing the cumulative total stockholder return on our common stock with the NASDAQ US Composite Index, the NASDAQ Biotechnology Index for the period covering from our IPO date of July 16, 2015, through the end of our fiscal year ended December 31, 2017. The graph assumes an investment of $100.00 made on July 16, 2015, in (i) our common stock, (ii) the stocks comprising the NASDAQ US Composite Index, and (iii) stocks comprising the NASDAQ Biotechnology Index. This graph is not soliciting material, is not deemed filed with the SEC and is not to be incorporated by reference into any filing by us under the Securities Act or the Exchange Act whether made before or after the date hereof and irrespective of any general incorporation language in any such filing. The graph assumes our closing sale price on July 16, 2015 of $20.00 per share as the initial value of our common stock and not the initial offering price to the public of $16.00 per share.

	7/16/15	9/30/15	12/31/15	3/31/16	6/30/16	9/30/16	12/31/16	3/31/17	6/30/17	9/30/17	12/31/17
Chiasma, Inc.	100.00	99.40	97.85	45.80	14.45	14.70	9.75	8.50	7.25	12.75	8.50
NASDAQ Composite	100.00	93.02	100.96	98.58	98.30	107.80	109.03	120.14	125.10	132.48	141.13
NASDAQ Biotechnology	100.00	82.27	91.33	73.20	71.49	78.65	72.88	79.81	83.66	90.24	85.34

Table of Contents

Our fiscal year ends on the last day of December each year; data in the above table reflects market values for our stock and NASDAQ and peer group indices as of the close of trading on the last trading day of the periods presented.

Securities authorized for issuance under equity compensation plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

None.

Use of Proceeds from Registered Securities

Use of Proceeds from Initial Public Offering of Common Stock

On July 21, 2015, we completed the sale of 7,319,750 shares of our common stock (inclusive of 954,750 shares of common stock sold by us pursuant to the full exercise of an option granted to the underwriters) in our IPO at a price to the public of $16.00 per share. The offer and sale of the shares in our IPO was registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-204949), which was filed with the SEC on June 15, 2015 and amended subsequently and declared effective by the SEC on July 15, 2015, and Form S-1MEF (File No. 333-205691), which was filed with the SEC on July 15, 2015 and automatically effective upon filing. Following the sale of the shares in connection with the closing of our IPO, the offering terminated. The offering did not terminate before all the securities registered in the registration statements were sold. Barclays Capital Inc. and Cowen and Company, LLC acted as joint book-running managers for the offering. William Blair & Company, L.L.C. and Oppenheimer & Co. Inc. acted as co-managers.

We raised approximately $106.5 million in net proceeds after deducting underwriting discounts and commissions and offering expenses payable by us. We invested the funds received in cash equivalents and other short-term investments in accordance with our investment policy.

In June 2016 and August 2016, we announced two separate corporate restructuring plans intended to focus our resources on the continued development of octreotide capsules for the maintenance treatment of adult acromegaly patients. As a result of the August 2016 reduction in workforce, we eliminated our research and discovery functions and are currently not investing in those areas.

We expect that our primary uses of capital will be associated with seeking regulatory approval of octreotide capsules in the United States and Europe, including clinical trial costs (including the international Phase 3 MPOWERED clinical trial that we initiated in March 2016 to support anticipated European regulatory approval of octreotide capsules and our international Phase 3 CHIASMA OPTIMAL clinical trial that we initiated in September 2017 to support United States regulatory approval of octreotide capsules), manufacturing of octreotide capsules for market consumption, if approved, legal and regulatory expenses related to seeking regulatory approval of octreotide capsules in the United States and Europe, compensation and related expenses, third-party clinical development services, legal and other regulatory expenses, and other general operating costs.

Issuer Purchases of Equity Securities

There were no repurchases of shares of common stock made during the year ended December 31, 2017.

91

Table of Contents

Item 6. Selected Financial Data

You should read the following selected consolidated financial data in conjunction with our consolidated financial statements and the related notes which are included 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. We have derived the consolidated statement of operations data for the years ended December 31, 2017, 2016, and 2015 and the consolidated balance sheet data as of December 31, 2017 and 2016, from our audited consolidated financial statements, which are included elsewhere in this Annual Report. We have derived the statement of operations data for the years ended December 31, 2014 and 2013, and the consolidated balance sheet data as of December 31, 2015, 2014 and 2013 from our audited consolidated financial statements, which are not included in this Annual Report. Our historical results for any prior period are not necessarily indicative of results to be expected for any future period.

	For the Years Ended December 31,				
	2017	2016	2015	2014	2013
	(in thousands except share and per share data)				
Consolidated Statement of Operations Data					
Revenue from license agreement	$	$	$	$ 13,166	$ 73,134
Operating expenses:					
General and administrative	9,146	21,815	16,456	3,469	8,065
Research and development	17,948	31,317	18,991	11,527	26,455
Restructuring charges	1,038	8,179			
Total operating expenses	28,132	61,311	35,447	14,996	34,520
Income (loss) from operations	(28,132)	(61,311)	(35,447)	(1,830)	38,614
Other expenses (income), net	(716)	(547)	300	5	1,209
Income (loss) before income taxes	(27,416)	(60,764)	(35,747)	(1,835)	37,405
Provision (benefit) for income taxes	(590)	347	161	176	1,224
Net income (loss)	(26,826)	(61,111)	(35,908)	(2,011)	36,181
Accretion of deemed liquidation related to Series D redeemable convertible preferred stock					(38,504)
Accretion of redeemable convertible preferred stock			(318)	(904)	(3,034)
Net loss attributable to common stockholders	$ (26,826)	$ (61,111)	$ (36,226)	$ (2,915)	$ (5,357)
Earnings per share attributable to common stockholders					
Basic	$ (1.10)	$ (2.51)	$ (3.25)	$ (66.21)	$ (125.29)

Diluted	$ (1.10)	$ (2.51)	$ (3.25)	$ (66.21)	$ (125.29)
Weighted-average shares outstanding:					
Basic	24,366,681	24,319,443	11,151,978	44,017	42,760
Diluted	24,366,681	24,319,443	11,151,978	44,017	42,760

Table of Contents

	2017	2016	December 31, 2015	2014	2013
			(in thousands)		
Consolidated Balance Sheet Data					
Cash and cash equivalents	$ 14,603	$ 37,013	$ 41,039	$ 40,160	$ 12,850
Marketable securities	52,336	55,971	107,715		
Current assets	68,707	95,094	151,085	40,472	13,288
Total assets	69,883	96,756	153,108	41,399	14,658
Current liabilities	6,745	8,400	6,514	4,318	14,465
Long-term liabilities	664	2,631	3,778	4,613	96
Total liabilities	7,409	11,031	10,292	8,931	14,561
Redeemable convertible preferred stock				104,486	70,732
Total stockholders equity (deficit)	62,474	85,725	142,816	(72,018)	(70,635)

Table of Contents

Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated financial statements and the accompanying notes thereto included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the Risk Factors section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company focused on improving the lives of patients who face challenges associated with their existing treatments for rare and serious chronic disease. Employing our proprietary Transient Permeability Enhancer, or TPE, technology platform, we seek to develop oral medications that are currently available only as injections. We are currently developing oral octreotide capsules, conditionally trade-named MYCAPSSA , our sole TPE platform-based clinical product candidate, in two Phase 3 clinical trials in adult patients for the treatment of acromegaly to potentially support regulatory approval in the United States and Europe. Acromegaly is a rare and debilitating condition that results in the body s production of excess growth hormone. Octreotide is an analog of somatostatin, a natural inhibitor of growth hormone secretion. We believe that octreotide capsules, if approved by regulatory authorities, will be the first somatostatin analog available for oral administration. Octreotide capsules have been granted orphan designation in the United States and the European Union for the treatment of acromegaly. The worldwide market for injectable somatostatin analogs is approximately $2.5 billion annually, of which we estimate approximately $775 million represents annual sales for the treatment of acromegaly. We retain worldwide rights to develop and commercialize octreotide capsules with no royalty obligations to third parties.

In September 2017, we initiated a third Phase 3 clinical trial for oral octreotide capsules for the maintenance therapy of adult patients with acromegaly following our agreement with the United States Food and Drug Administration, or the FDA, on the design of the trial, reached through a Special Protocol Assessment, or SPA, in August 2017. The trial, referred to as CHIASMA OPTIMAL, is a randomized, double-blind, placebo-controlled, nine-month trial expected to enroll 50 adult acromegaly patients designed to support regulatory approval of octreotide capsules in the United States. We expect to release top-line data from this trial by the end of 2019. We are also currently conducting an international Phase 3 clinical trial, referred to as MPOWERED, of oral octreotide capsules for the maintenance treatment of adult patients with acromegaly to support regulatory approval in Europe. The MPOWERED trial is a global, randomized, open-label and active-controlled 15-month trial expected to enroll approximately 130 adult acromegaly patients, of which we expect to randomize at least 80 patients who are responders to octreotide capsules following a six-month run-in to either octreotide capsules or injectable somatostatin receptor ligands (octreotide or lanreotide), and then followed for an additional nine months. We currently expect to release top-line data from the MPOWERED trial in 2020.

We were incorporated in 2001 and commenced active operations in the same year. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our TPE technology, identifying potential drug candidates, undertaking nonclinical studies and, beginning in 2010, conducting clinical trials and preparing for regulatory submissions. To date, we have financed our operations primarily through private placements, funding received from a licensing agreement, a loan agreement and our initial public offering. We have no products approved for sale and all of our historical revenue has been related to one license agreement, which has been terminated. Since our inception and through December 31, 2017, we have raised an aggregate of $366.2 million to fund our operations, of which $86.3 million was through our license agreement with F. Hoffmann-La Roche Ltd.

and Hoffmann-La Roche Inc., collectively Roche, $106.5 million was from issuing shares of common stock in our initial public offering, or IPO, $161.4 million was from the

Table of Contents

issuance of private securities and $12.0 million was from borrowings under a loan agreement. In 2013, using proceeds from the Roche license agreement, we repaid all outstanding borrowings under our loan agreement and paid an aggregate of $55.0 million in cash as partial consideration for the redemption of certain shares of our redeemable preferred stock. As of December 31, 2017, our consolidated cash, cash equivalents and marketable securities were $66.9 million, of which $0.2 million was held by Chiasma (Israel) Ltd., our wholly owned Israeli subsidiary.

We have incurred significant operating losses since our inception. Our net loss was $26.8 million and $61.1 million for the years ended December 31, 2017 and 2016, respectively. As of December 31, 2017, we had an accumulated deficit of $205.4 million. We expect to incur significant operating losses over the next several years. These losses, combined with prior losses will continue to have an adverse effect on our cash resources, stockholders equity and working capital. We expect to continue to conduct the international Phase 3 MPOWERED clinical trial of octreotide capsules in acromegaly that we initiated in March 2016 to support potential regulatory approval in Europe and plan to continue our Phase 3 CHIASMA OPTIMAL clinical trial of octreotide capsules in acromegaly that we initiated in September 2017 to support potential regulatory approval in the United States. We expect the release of top-line CHIASMA OPTIMAL data by the end of 2019 and we expect the release of top-line MPOWERED data in 2020. Clinical development timelines, the probability of success and development costs can differ materially from expectations.

In June and August 2016, we announced two separate corporate restructuring plans intended to focus our resources on the continued development of octreotide capsules for the maintenance treatment of adult acromegaly patients. As a result of the August 2016 reduction in workforce, we eliminated our research and discovery functions and are currently not investing in those areas. Because of the numerous risks and uncertainties facing our company and associated with developing and commercializing pharmaceutical products generally, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings and debt financings, and we may also opportunistically consider license and collaboration agreements with potential partners. We may be unable to raise capital when needed or on attractive terms, or to enter into collaboration agreements, which could force us to delay, limit, reduce or terminate our product development or future commercialization efforts. We will need to generate significant revenues to achieve profitability, which we may not be able to achieve.

Roche License Agreement

In December 2012, we signed a license agreement with Roche, which went into effect on January 2013. Pursuant to the license agreement, we granted Roche an exclusive, non-transferable license to all intellectual property related to octreotide capsules. Under the terms of the license, Roche obtained worldwide rights to research, develop, make, import, export, sell, market or distribute the commercial product. We retained certain responsibilities for research and development activities under a joint development plan.

In July 2014, Roche terminated the license agreement. Pursuant to the termination of the license agreement, we are not entitled to further payments from Roche, Roche has no remaining rights to octreotide capsules and we retain all rights to octreotide capsules and all related intellectual property. Subsequent to the termination, we purchased from Roche active pharmaceutical ingredient, or API, supplies to continue the development and manufacturing of octreotide capsules, together with Roche s proposed trade name, Mycapssa for octreotide capsules, for an aggregate amount of $5.1 million, payable in three annual installments of $1.7 million beginning in 2016. We made the $1.7 million annual payments in March of 2018, 2017, and 2016. Other than these payments, we have no further financial or operational obligations to Roche.

95

Table of Contents

Financial Overview

Research and Development

Research and development expenses consist of expenses incurred in performing research and development activities, including compensation and benefits for full-time research and development employees, an allocation of facilities expenses, overhead expenses, nonclinical pharmacology studies, manufacturing process-development and scale-up activities, clinical trial and related clinical manufacturing expenses, fees paid to contract research organizations, or CROs, investigative sites, and other external expenses. In the early phases of development, our research and development costs included expanding our technology platform as well as early development of specific product candidates. The majority of our research and development expenses has been spent on the development of octreotide capsules, including the manufacturing of clinical trial material, manufacturing process development and validation regulatory and clinical activities, and our TPE platform. We expense research and development costs as incurred.

As a result of the August 2016 reduction in workforce, we eliminated our research and discovery functions and are currently not investing in those areas. We continue to invest in the clinical development of octreotide capsules. Product candidates in late stages of development generally have higher development costs than those in earlier stages of development, primarily due to the increased size and duration of late-stage clinical trials. We plan to continue our international Phase 3 CHIASMA OPTIMAL clinical trial of octreotide capsules in acromegaly that we initiated in September 2017 to support potential regulatory approval in the United States. We also expect to continue to conduct our international Phase 3 MPOWERED clinical trial of octreotide capsules in acromegaly that we initiated in March 2016 to support potential regulatory approval in Europe. The successful development of octreotide capsules are highly uncertain.

General and Administrative

General and administrative expenses consist primarily of salaries and related benefits, including stock-based compensation, related to our executive, finance, legal, marketing and support functions. Other general and administrative expenses include facility-related costs not otherwise allocated to research and development expenses, travel expenses for our general and administrative personnel and professional fees for auditing, tax, and corporate and intellectual property legal services.

Marketing expenses consist of professional fees related to preparation for the potential commercialization of octreotide capsules, if approved, as well as salaries and related benefits for commercial employees. In anticipation of marketing approval of our NDA, and prior to the receipt of the CRL in April 2016, we accelerated our preparation for commercialization of octreotide capsules. Following the June 2016 restructuring plan and the termination of primarily all of our commercial personnel, these expenses were significantly reduced throughout 2016. Our marketing expenses in 2017 were immaterial and are expected to continue to be immaterial while our primary business activity involves the conduct of clinical trials.

Restructuring Charges

Restructuring charges consist of employee severance benefits and related costs, contract termination fees, asset write-offs resulting from restructuring plans, suspension fees associated with commercial manufacturing agreements, lease termination fees, and other expenses associated with restructuring our operations.

Other (Income) Expenses, Net

Other income, net consists mainly of interest income earned on our investments, net of interest incurred on our obligation related to the acquisition of API and trade name MYCAPSSA from Roche.

Table of Contents

Provision for Income Taxes

We are subject to federal and state income taxes for earnings generated in the United States, and foreign taxes on earnings of our wholly-owned Israeli subsidiary. Our consolidated tax expense is primarily affected by the mix of our foreign subsidiary permanent items, discrete items, and unrecognized tax benefits and to a lesser extent our taxable income (loss) in the United States.

Results of Operations

Comparison for the Years Ended December 31, 2017 and 2016

The following tables set forth, for the periods indicated, our results of operations and the change between the specified periods expressed as a percent increase or decrease:

Research and Development

	2017	2016	$ Change	% change
		($ in thousands)		
Research and development	$ 17,948	$ 31,317	$ (13,369)	(43%)

During the year ended December 31, 2017, our total research and development expenses decreased by $13.4 million to $17.9 million. This decrease was primarily due to approximately $7.4 million of API purchases and pre-commercial manufacturing validation activities during 2016, that did not reoccur in 2017, as well as reduced compensation-related costs and other research and development program efforts following the reductions of force in June and August 2016. These decreases were partially offset by an increase in clinical trial costs of $1.3 million in 2017.

General and Administrative

	2017	2016	$ Change	% change
		($ in thousands)		
General and administrative	$ 9,146	$ 21,815	$ (12,669)	(58%)

For the year ended December 31, 2017, our general and administrative expenses decreased by $12.7 million to $9.1 million. This decrease was primarily due to the reduction in pre-commercial activity expenditures following the CRL, as well as the June and August 2016 reductions in force of substantially all of our commercial personnel and certain administrative functions.

Restructuring Charges

In November 2017, we finalized the termination of our lease agreement on our 24,000 square foot office facility in Waltham, MA which we no longer required following the 2016 workforce reductions. As a result, we recorded approximately $1.0 million of restructuring expenses during the year ended December 31, 2017, which consisted of a

lease termination payment of $1.0 million, the write-off of office furniture and equipment of $0.4 million offset by the release of deferred rent liabilities of $0.4 million associated with the terminated lease.

In June 2016, we announced a corporate restructuring plan, including an immediate reduction of approximately 33% of our workforce, including substantially all of our commercial personnel. In August 2016, we announced a second corporate restructuring plan, including an immediate reduction of approximately 44% of our remaining workforce. In aggregate, these restructuring plans resulted in a reduction to our workforce of more than 60% since May 1, 2016. As a result of the August reduction in force, we no longer required the research lab and additional office space of the Israel facility and we were able to early terminate the Israel lease in November

Table of Contents

2016. Accordingly, we recorded restructuring charges totaling $8.2 million during the year ended December 31, 2016 which consisted of employee severance benefits and related costs of $2.2 million, manufacturing commitment-related suspension fees of $4.5 million, non-cash restructuring charges of $0.8 million resulting from the impairment of leasehold improvements of $1.7 million offset by the forgiveness of tenant allowances received under the lease of $0.9 million and non-cash restructuring charges related to the impairment of capitalized commercial software and laboratory equipment of $0.7 million.

Other (Income) Expense, net

Other income totaled $0.7 million for the year ended December 31, 2017, compared to $0.5 million for the year ended December 31, 2016. The improvement was driven by interest income generated from increased yields on our cash equivalents and marketable securities and a decrease in the imputed interest expense associated with the lower remaining obligation related to the acquisition of API and trade name MYCAPSSA from Roche.

Provision (Benefit) for Income Taxes

Our total tax benefit was $0.6 million for the year ended December 31, 2017, representing an effective tax rate of 2.16%, as compared to a tax provision of $0.3 million for the year ended December 31, 2016, representing an effective tax rate of (0.6%).

Our deferred tax assets at December 31, 2017 and 2016 were approximately $24,000 and $86,000, respectively. Deferred tax assets were reported net of valuation allowances of $40.0 million and $49.1 million at December 31, 2017 and 2016, respectively, primarily as a result of the recording of a full valuation allowance against U.S. net operating loss, or NOL, carryforwards, as we believe it is more likely than not that we will not be able to generate sufficient future taxable income to absorb them. At December 31, 2017, we had U.S. federal NOL carryforwards of $146.4 million. The U.S. federal NOL carryforwards expire at various dates through 2037. At December 31, 2017, we had no Israeli NOL carryforwards. At December 31, 2017, we had approximately $1.0 million of U.S. federal alternative minimum tax credit carryforwards that do not expire. Federal tax reform, enacted in December 2017, allows for U.S. federal alternative minimum tax credit carryforwards to be refunded between 2018 and 2021. We have a history of generating losses and are forecasting that we will not generate taxable income through 2021 which would otherwise limit our ability to realize the U.S. Federal alternative minimum tax credit. Accordingly, we have recorded the U.S. Federal alternative minimum tax credit as a benefit to the income tax provision.

Our effective tax rate differs from the statutory rate each year mainly due to a full valuation allowance maintained against U.S. deferred tax assets and due to lower tax rates applied to income of our Israeli subsidiary.

Comparison for the Years Ended December 31, 2016 and 2015

The following tables set forth, for the periods indicated, our results of operations and the change between the specified periods expressed as a percent increase or decrease:

Research and Development

	2016	2015	$ Change	% Change
		($ in thousands)		

Research and development	$ 31,317	$ 18,991	$ 12,326	65%

During the year ended December 31, 2016, our total research and development expenses increased by $12.3 million, or 65%, compared to the prior year, primarily due to approximately $7.4 million of API purchases during the year ended December 31, 2016, our ongoing MPOWERED Phase 3 clinical trial of octreotide capsules for the treatment of acromegaly, activities associated with the manufacturing process validation, and an increase in compensation-related expenses due to the hiring of research and development employees.

Table of Contents

General and Administrative

	2016	2015	$ Change	Percent change
		($ in thousands)		
Marketing	$ 7,672	$ 7,317	$ 355	5%
General and administrative	14,143	9,139	5,004	55%
Total general and administrative expenses	$ 21,815	$ 16,456	$ 5,359	33%

During the year ended December 31, 2016, our marketing expenses increased by $0.4 million to $7.7 million. This increase was primarily due to pre-commercial activities related to octreotide capsules and greater compensation-related expenses associated with our expanded U.S. marketing and sales leadership team hired in anticipation of our expected FDA approval of octreotide capsules in April 2016 for commercialization in the United States, which did not occur.

During the year ended December 31, 2016, our general and administrative expenses increased by $5.0 million to $14.1 million. This increase was primarily due to greater compensation-related expenses associated with our expanded U.S. office as well as increased professional and consulting fees associated with being a public company.

Restructuring Charges

In June 2016, we announced a corporate restructuring plan, including an immediate reduction of approximately 33% of our workforce, including substantially all of our commercial personnel. In August 2016, we announced a second corporate restructuring plan, including an immediate reduction of approximately 44% of our remaining workforce. In aggregate, these restructuring plans resulted in a reduction to our workforce of more than 60% since May 1, 2016. As a result of the August reduction in force, we no longer required the research lab and additional office space of the Israel facility and we were able to early terminate the Israel lease in November 2016. Accordingly, we recorded restructuring charges totaling $8.2 million during the year ended December 31, 2016 which consisted of employee severance benefits and related costs of $2.2 million, manufacturing commitment-related suspension fees of $4.5 million, non-cash restructuring charges of $0.8 million resulting from the impairment of leasehold improvements of $1.7 million offset by the forgiveness of tenant allowances received under the lease of $0.9 million and non-cash restructuring charges related to the impairment of capitalized commercial software and laboratory equipment of $0.7 million.

Other (Income) Expense, net

Other income totaled $0.5 million for the year ended December 31, 2016, compared to $0.3 million of other expenses for the year ended December 31, 2015. The improvement was driven by interest income generated from the investment of our IPO proceeds and a decrease in the imputed interest associated with the long-term obligation related to the acquisition of API and trade name MYCAPSSA from Roche.

Provision for Income Taxes

Our total tax provision was $0.3 million for the year ended December 31, 2016, representing an effective tax rate of (0.6%), as compared to a tax provision of $0.2 million for the year ended December 31, 2015, representing an

effective tax rate of (0.5%).

Our deferred tax assets at December 31, 2016 and 2015 were approximately $86,000 and $70,000, respectively. Deferred tax assets were reported net of valuation allowances of $49.1 million and $24.8 million at December 31, 2016 and 2015, respectively, primarily as a result of the recording of a full valuation allowance against NOL carryforwards, as we believe it is more likely than not that we will not be able to generate sufficient future

Table of Contents

taxable income to absorb them. At December 31, 2016, we had federal NOL carryforwards of $126.9 million. The federal NOL carryforwards expire at various dates through 2035. At December 31, 2016, we had no Israeli NOL carryforwards. At December 31, 2016, we had approximately $1.0 million of federal alternative minimum tax credit carryforwards that do not expire.

Our effective tax rate differs from the statutory rate each year mainly due to a full valuation allowance maintained against U.S. deferred tax assets and due to lower tax rates applied to income of our Israeli subsidiary.

Liquidity and Capital Resources

Since our inception and through December 31, 2017, we have raised an aggregate of $366.2 million to fund our operations, of which $86.3 million was through our license agreement with Roche, approximately $106.5 million was from selling shares of common stock in our IPO, $161.4 million was from the issuance of private securities, and $12.0 million was from borrowings under a loan agreement. In March 2013, using proceeds from the Roche license agreement, we repaid all outstanding borrowings under our loan agreement and paid an aggregate of $55.0 million in cash as partial consideration for the redemption of certain shares of our preferred stock.

As of December 31, 2017, our cash and cash equivalents were $14.6 million, of which $0.2 million was held by our Israeli subsidiary. In addition, as of December 31, 2017, we have $52.3 million invested in short-term marketable securities.

Plan of Operations and Future Funding Requirements

We expect that our primary uses of capital will be associated with seeking regulatory approval of octreotide capsules in the United States and Europe, including clinical trial costs (including our international Phase 3 CHIASMA OPTIMAL clinical trial that we initiated in September 2017 to support regulatory approval of octreotide capsules in the United States and our international Phase 3 MPOWERED clinical trial that we initiated in March 2016 to support regulatory approval of octreotide capsules in Europe), manufacturing of octreotide capsules for market consumption, if approved, legal and regulatory expenses related to seeking regulatory approval of octreotide capsules in the United States and Europe, compensation and related expenses, third-party clinical development services, legal and other regulatory expenses, and other general operating costs.

In June 2016, we announced a corporate restructuring plan intended to focus our resources on the continued development of octreotide capsules for the potential maintenance treatment of adult acromegaly patients. This plan included a reduction of approximately 33% of our workforce at the time, including substantially all of our commercial personnel. In August 2016, we announced a second corporate restructuring plan that included the reduction of approximately 44% of our remaining workforce. In aggregate, these restructuring plans resulted in a reduction to our workforce of more than 60% since May 1, 2016. In November 2017, we terminated the lease agreement on our 24,000 square foot office facility in Waltham, MA which we no longer required following the 2016 workforce reductions. We currently expect our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations through the anticipated release of top-line data from our Phase 3 CHIASMA OPTIMAL trial by the end of 2019 while supporting our Phase 3MPOWERED trial in parallel. We cannot estimate the actual amounts necessary to successfully complete the development and commercialization of octreotide capsules, if at all, or whether, or when, we may achieve profitability. Our future capital requirements will depend on many factors, including, but not limited to:

the costs, timing and outcome of the development and regulatory review of octreotide capsules;

the progress and results of our ongoing clinical trial of octreotide capsules or any future clinical trials or studies we may conduct;

the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for octreotide capsules and any other future product candidates for which we receive marketing approval;

Table of Contents

proceeds, if any, received from commercial sales of octreotide capsules and any future product candidates for which we receive marketing approval;

the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and

the extent to which we develop, acquire or in-license other product candidates and technologies or explore or consummate other strategic transactions.

Until such time, if ever, as we can generate substantial product sales, we expect to finance our cash needs through a combination of equity offerings and debt financings and we may opportunistically consider license and collaboration arrangements. We are currently eligible to file a shelf registration statement and believe that shelf registration statements can contribute, when used, to greater financial flexibility. To that end, we plan to file a shelf registration statement on Form S-3 with the Securities and Exchange Commission in the near future. To the extent that we raise additional capital through future issuance of equity or debt, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through collaboration arrangements, we may have to relinquish valuable rights to our current or future product candidates, exploratory programs, technologies or future revenue streams on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts of octreotide capsules or grant rights to develop and market future potential product candidates that we would otherwise prefer to develop and market ourselves.

Cash Flows

The following is a summary of cash flows for the years ended December 31, 2017 and 2016:

	2017	2016
	($ in thousands)	
Cash flows provided by (used in):		
Operating activities	$ (24,424)	$ (51,964)
Investing activities	3,712	49,033
Financing activities	(1,698)	(1,095)

Operating Activities

Net cash used in operating activities was $24.4 million in 2017, and primarily consisted of $26.8 million in net loss, adjusted for non-cash items of $2.8 million (primarily stock-based compensation of $3.5 million and partially offset by benefit for deferred income taxes) and was offset by working capital decreases of $0.4 million (primarily driven by the decrease in accounts payable and accrued expenses and partially offset by the decreases in prepaid and other current assets and other assets). Net cash used in operating activities was $52.0 million in 2016, and primarily consisted of $61.1 million in net loss, adjusted for non-cash items of $5.4 million (primarily stock-based compensation of $3.3 million and non-cash restructuring charges of $1.5 million) and was offset by working capital increases of $3.7 million (primarily driven by the increase in accounts payable, accrued expenses, other liabilities and the decrease in prepaid and other current assets).

Investing Activities

Net cash provided by investing activities was $3.7 million in 2017, primarily related to the net maturities of marketable securities. Net cash provided by investing activities was $49.0 million in 2016, primarily related to the net maturities of marketable securities and was partially offset by $3.0 million of purchases of property and equipment.

Table of Contents

Financing Activities

Net cash used in financing activities was $1.7 million in 2017, related to the second $1.7 million installment payment on the termination of the Roche license agreement. Net cash used in financing activities was $1.1 million in 2016, primarily related to the first $1.7 million installment payment related to the termination of the Roche license agreement and was partially offset by $0.6 million of proceeds from stock option exercises.

Contractual Obligations and Contingent Liabilities

The following summarizes our significant contractual obligations as of December 31, 2017:

Contractual Obligations	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
		($ in thousands)			
Operating leases	$ 370	$ 156	$ 214	$	$
Short term purchase obligations	1,700	1,700			
Total contractual obligations	$ 2,070	$ 1,856	$ 214	$	$

Operating Leases. This amount represents future minimum lease payments under non-cancelable operating leases in effect as of December 31, 2017 for our current and future facilities in the U.S. and Israel. The minimum lease payments do not include common area maintenance charges or real estate taxes.

Short-term Purchase Obligation. Upon termination of the Roche agreement in 2014, we purchased API supplies from Roche to continue the development and manufacturing of octreotide capsules and Roche s proposed trade name for octreotide capsules for an aggregate amount of $5.1 million payable in three equal annual installments of $1.7 million beginning in 2016. We made the $1.7 million annual payments in March of 2018, 2017, and 2016. We have no further obligations to Roche upon full payment of these amounts.

The table excludes potential payments we may be required to make under manufacturing and CRO agreements as the timing of when these payments will be made is uncertain and the payments are contingent upon the initiation and completion of future activities.

Critical Accounting Policies and Use of Estimates

Our management s discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of consolidated financial statements in conformity with GAAP requires us to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. We base these estimates and assumptions on historical experience when available, and on various factors that we believe to be reasonable under the specific circumstances. Significant estimates relied upon in preparing the accompanying consolidated financial statements include, but are not limited to, the fair value of common stock and other equity instruments, accounting for stock-based compensation, present value of long-term purchase obligation, income taxes, and accounting for certain accruals. We assess these estimates on an ongoing basis; however, actual results could materially differ from those estimates.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are critical to the process of making significant judgments and estimates in the preparation of our consolidated financial statements and understanding and evaluating our reported financial results.

Table of Contents

Clinical trial costs

Clinical trial costs are a component of research and development expenses. We accrue and expense clinical trial activities performed by third parties on an evaluation of the progress to completion of specific tasks using data such as hours spent in performance of services, patient enrollment, clinical site activation, and other information provided to us by our vendors. We make estimates of our clinical trial accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. If timelines or contracts are modified based upon changes in the clinical trial protocol or scope of work to be performed, we assess our estimates of accrued expenses accordingly.

If we do not identify costs that we have begun to incur, or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Stock-based Compensation

We account for all stock-based compensation to employees and nonemployees based on their fair values on the date of grant. The fair value of stock-based awards to nonemployees is remeasured as the award vests. For employee stock-based awards with only service conditions, we recognize compensation on a straight-line basis over the requisite service period, which is usually the vesting period of the award, net of any actual forfeitures.

We determine the fair value of stock options by using the Black-Scholes option pricing model. This model requires the input of several assumptions such as the expected option term, the expected risk-free interest rate over the expected option term, the expected volatility of our stock price over the expected option term, and the expected dividend yield over the expected option term. The computation of expected volatility is based on an average historical share price volatility based on an analysis of reported data for a peer group of comparable publicly traded companies, which were selected based upon industry similarities. The interest rate for periods within the expected term of the award is based on the U.S. Treasury risk-free interest rate in effect at the time of grant. The expected lives of the options were estimated using the simplified method. For options granted to non-employees, the expected life of the option used is the contractual term of each such option. All other assumptions used to calculate the grant date fair value are generally consistent with the assumptions used for options granted to employees. Stock-based compensation expense for awards granted to non-employees is adjusted as the award vests to reflect the current fair value of such awards, and is recognized using an accelerated attribution model.

Income Taxes

The consolidated financial statements presented elsewhere in this Annual Report on Form 10-K reflect provisions for federal, state, local and foreign income taxes. Deferred tax assets and liabilities represent future tax consequences of temporary differences between the financial statement carrying amounts and the tax basis of assets and liabilities and for loss carryforwards using enacted tax rates expected to be in effect in the years in which the differences reverse. A valuation allowance is recorded when it is more likely than not that some or all of the deferred tax assets will not be realized. We cannot be certain that future U.S. taxable income will be sufficient to realize our deferred tax assets and, accordingly, a full valuation allowance has been provided against our U.S. net deferred tax assets.

We evaluate the tax positions we have taken when preparing our federal, state, local and foreign income tax returns, and determine whether it is more likely than not that a tax position will be sustained upon examination. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The tax benefit to be recognized for any tax position that meets the more likely than not recognition threshold is calculated

as the largest amount that is more than 50% likely of being realized upon resolution of the contingency. As of December 31, 2017 and 2016, we have provided a liability of $0.5 million and $0.5 million, respectively. We account for interest and penalties related to uncertain tax positions as part of our other expenses.

Table of Contents

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of 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. Thus, an emerging growth company can 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 extended transition period, and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for public companies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of December 31, 2017, we had $14.6 million in cash and cash equivalents, consisting of cash in checking accounts at U.S. and Israeli banking institutions as well as money market funds and short term corporate notes. In addition, we had $52.3 million of marketable securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. An immediate 100 basis point change in interest rates would cause a decrease in the value of short-term investments of $0.2 million. As of December 31, 2017, we did not have any outstanding borrowings so that we are not exposed to interest rate risk associated with credit facilities.

In addition, we are subject to currency risk for balances held, or denominated, in currencies other than U.S. dollars. We work to maintain all balances in U.S. dollars until payment in other currencies is required to minimize this currency risk. Fluctuations in the exchange rate between the U.S. dollar and each of the Euro, GBP and NIS over the past 24 months has been approximately 9%, 9% and 11%, respectively. As of December 31, 2017, we held $0.2 million in Israeli banks and petty cash funds to support our Israeli operations, the majority of which is denominated in U.S. dollars. We contract with CROs internationally, primarily for the execution of clinical trials and manufacturing activities. Transactions with these providers are settled in U.S. dollars, Euros or GBP and, therefore, we believe that we have only minimal exposure to foreign currency exchange risks. We do not hedge against foreign currency risks.

We do not believe that inflation and changing prices had a significant impact on our results of operations for any periods presented herein.

Item 8. Financial Statements and Supplementary Data

See the consolidated financial statements filed as part of this Annual Report on Form 10-K as listed under Item 15 below.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

Not Applicable.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) are designed only to provide reasonable assurance that they will meet their objectives. Under the supervision and with the

Table of Contents

participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness, as of December 31, 2017, of the design and operation of our disclosure controls and procedures, as such term is defined in Exchange Act Rules 13a-15(e) and 15d-15(e). Based on this evaluation, our principal executive officer and principal financial officer has concluded that, as of such date, our disclosure controls and procedures are effective to ensure that information required to be disclosed by us in our Exchange Act reports is recorded, processed, summarized, and reported within the time periods specified in the SEC s rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure.

Management s Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rule 13a-15(f). Our internal control over financial reporting is designed to provide reasonable assurance to our management and board of directors regarding the preparation and fair presentation of published financial statements. A control system, no matter how well designed and operated, can only provide reasonable, not absolute, assurance that the objectives of the control system are met. Because of these inherent limitations, management does not expect that our internal controls over financial reporting will prevent all error and all fraud. Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in Internal Control-Integrated Framework issued in 2013 by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under the framework in Internal Control-Integrated Framework, our management concluded that our internal control over financial reporting was effective as of December 31, 2017.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) or 15d-15(d)) during the quarter ended December 31, 2017 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information
Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance
The information required under this item is incorporated herein by reference to the Company s definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company s fiscal year ended December 31, 2017.

We intend to disclose on our website any amendments to, or waivers from, our Code of Business Conduct and Ethics that are required to be disclosed pursuant to the rules of the SEC. Information contained on, or connected to, our website is not incorporated by reference into this Form 10-K and should not be considered part of this report or any

other filing that we make with the SEC.

Item 11. Executive Compensation

The information required under this item is incorporated herein by reference to the Company s definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company s fiscal year ended December 31, 2017.

Table of Contents

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required under this item is incorporated herein by reference to the Company s definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company s fiscal year ended December 31, 2017.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required under this item is incorporated herein by reference to the Company s definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company s fiscal year ended December 31, 2017.

Item 14. Principal Accounting Fees and Services

The information required under this item is incorporated herein by reference to the Company s definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company s fiscal year ended December 31, 2017.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) 1. Consolidated Financial Statements.

For a list of the consolidated financial statements included herein, see Index on page F-1 of this report.

2. Financial Statement Schedules.

All required information is included in the financial statements or notes thereto.

3. List of Exhibits.

See the Exhibit Index in Item 15(b) below.

7(b) Exhibit Index.

Table of Contents

EXHIBIT INDEX

Exhibit No.	
3.1	Amended and Restated Certificate of Incorporation of the Company, incorporated by reference from our Current Report on Form 8-K filed on July 21, 2015
3.2	Amended and Restated Bylaws of the Company, incorporated by reference from our Current Report on Form 8-K filed on July 21, 2015
4.1	Form of Common Stock certificate of the Company, incorporated by reference from our Amendment No. 1 to Registration Statement on Form S-1/A filed on July 6, 2015 (File No. 333-204949)
4.2	Amended and Restated Investors Rights Agreement, by and between the Company and the Investors named therein, dated as of December 16, 2014, incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
4.3	Form of Warrant to Purchase Shares of Common Stock (issued in connection with the Company s Series D preferred stock financing), incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
4.4	Form of Warrant to Purchase Shares of Common Stock (issued in connection with the Company s Series E preferred stock financing), incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
10.1	Israeli Stock Option Plan 2003 and forms of agreements thereunder, incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
10.2	2015 Stock Option and Incentive Plan and forms of agreement thereunder, incorporated by reference from our Amendment No. 1 to Registration Statement on Form S-1/A filed on July 6, 2015 (File No. 333-204949)
10.3	2015 Employee Stock Purchase Plan, incorporated by reference from our Amendment No. 1 to Registration Statement on Form S-1/A filed on July 6, 2015 (File No. 333-204949)
10.4	Senior Executive Cash Incentive Bonus Plan, incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
10.5	Amended and Restated Employment Agreement dated as of September 27, 2016 by and between the Company and Mark J. Fitzpatrick, incorporated by reference from our Current Report on Form 8-K filed on September 30, 2016
10.6	Employment Agreement dated as of December 16, 2014, as amended, by and between Chiasma (Israel) Ltd. and Roni Mamluk, incorporated by reference from our Registration Statement on Form S-1 filed on June 15, 2015 (File No. 333-204949)
10.7	Amendment to Employment Agreement, dated as of November 15, 2016, by and between Chiasma (Israel) Ltd. And Roni Mamluk, incorporated by reference from our Annual Report on Form 10-K filed on March 16, 2017
10.8	Amendment to Employment Agreement, dated as of December 14, 2016, by and between Chiasma (Israel) Ltd. And Roni Mamluk, incorporated by reference from our Annual Report on Form 10-K filed

	on March 16, 2017
10.9	Separation Settlement Agreement and Release, dated as of March 31, 2017, by and between Chiasma (Israel) Ltd. and Roni Mamluk, incorporated by reference from our Current Report on Form 8-K filed on June 19, 2017
10.10	Director Agreement, dated as of April 1, 2017, by and between Chiasma (Israel) Ltd. and Roni Mamluk, incorporated by reference from our Current Report on Form 8-K filed on June 19, 2017

Table of Contents

Exhibit No.	
10.11	Amended and Restated Employment Agreement dated as of February 23, 2018 by and between the Company and Drew Enamait, incorporated by reference from our Current Report on Form 8-K filed on February 28, 2018
10.12	Form of Indemnification Agreement, to be entered into between the Company and its directors and officers, incorporated by reference from our Amendment No. 1 to Registration Statement on Form S-1/A filed on July 6, 2015 (File No. 333-204949)
10.13	Amended and Restated Non-Employee Director Compensation Policy, incorporated by reference from our Quarterly Report on Form 10-Q filed on May 5, 2017
10.14	Sublease dated as of November 20, 2015 by and between the Company and Cimpress USA Incorporated (f/k/a Vistaprint USA, Incorporated), incorporated by reference from our Annual Report on Form 10-K filed on March 17, 2016
10.15	Sublease Termination Agreement dated as of November 8, 2017 by and between the Company and Cimpress USA Incorporated, incorporated by reference from our Current Report on Form 8-K filed on November 11, 2017
10.16*	Lease dated as of November 15, 2017 by and between the Company and NWALP TPOP Property Owner LLC
21.1*	Subsidiaries of the Company
23.1*	Consent of Deloitte & Touche LLP
23.2*	Consent of Kost Forer Gabbay & Kasierer
31.1*	Certification of the Chief Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certification of the Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101	Interactive Data Files regarding (a) our Consolidated Balance Sheets as of December 31, 2017 and 2016, (b) our Consolidated Statements of Operations and Comprehensive Income (Loss) for the Years Ended December 31, 2017, 2016 and 2015, (c) our Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders Equity (Deficit) for the Year Ended December 31, 2015, (d) our Consolidated Statement of Stockholders Equity for the Years Ended December 31, 2017 and 2016, (e) our Consolidated Statements of Cash Flows for the Years Ended December 31, 2017, 2016 and 2015 and (f) the Notes to such Consolidated Financial Statements

Indicates a management contract or compensatory plan.

* Filed herewith.

** Furnished herewith.

Item 16. Form 10-K Summary

None.

108

Table of Contents

SIGNATURES

Pursuant to the requirements of the Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Waltham, Commonwealth of Massachusetts, on March 20, 2018.

Chiasma, Inc.

By: /s/ *Mark J. Fitzpatrick*
Mark J. Fitzpatrick
President, Chief Executive Officer and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ *Mark J. Fitzpatrick* Mark J. Fitzpatrick	President, Chief Executive Officer and Director *(Principal Executive Officer and Principal Financial Officer)*	March 20, 2018
/s/ *Drew Enamait* Drew Enamait	Vice President, Finance and Administration *(Principal Accounting Officer)*	March 20, 2018
/s/ *David Stack* David Stack	Director	March 20, 2018
/s/ *Todd Foley* Todd Foley	Director	March 20, 2018
/s/ *Bard Geesaman, M.D., Ph.D.* Bard Geesaman, M.D., Ph.D.	Director	March 20, 2018
/s/ *Roni Mamluk, Ph.D.* Roni Mamluk, Ph.D.	Director	March 20, 2018
/s/ *Scott Minick* Scott Minick	Director	March 20, 2018

/s/ *John Scarlett, M.D.*	Director	March 20, 2018
John Scarlett, M.D.		
/s/ *John F. Thero*	Director	March 20, 2018
John F. Thero		

Table of Contents

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm Deloitte & Touche LLP	F-2
Report of Independent Registered Public Accounting Firm Kost Forer Gabbay & Kasierer	F-3
Consolidated Balance Sheets	F-4
Consolidated Statements of Operations	F-5
Consolidated Statements of Comprehensive Income (Loss)	F-6
Consolidated Statement of Redeemable Convertible Preferred Stock and Stockholders Equity (Deficit)	F-7
Consolidated Statements of Stockholders Equity	F-8
Consolidated Statements of Cash Flows	F-9
Notes to Consolidated Financial Statements	F-10

Table of Contents

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Chiasma, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Chiasma, Inc. and subsidiaries (the Company) as of December 31, 2017 and 2016, the related consolidated statements of operations, comprehensive income (loss), stockholders equity and cash flows for each of the two years in the period ended December 31, 2017, and the related notes (collectively referred to as the financial statements). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2017, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company s management. Our responsibility is to express an opinion on the Company s financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company s internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Deloitte & Touche LLP

Boston, Massachusetts

March 20, 2018

We have served as the Company s auditor since 2016.

Table of Contents

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Shareholders of Chiasma Inc.

We have audited the accompanying consolidated balance sheet of Chiasma Inc. as of December 31, 2015, and the related consolidated statements of operations, comprehensive income (loss), redeemable convertible preferred stock and shareholders equity (deficit) and cash flows for the year ended December 31, 2015. These financial statements are the responsibility of the Company s management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company s internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company s internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Chiasma Inc. at December 31, 2015, and the consolidated results of their operations and their cash flows for the year ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Kost Forer Gabbay & Kasierer

KOST FORER GABBAY & KASIERER

A Member of Ernst & Young Global

Tel-Aviv, Israel

March 17, 2016

Table of Contents

CHIASMA, INC.

CONSOLIDATED BALANCE SHEETS

	As of December 31,	
	2017	2016
	(in thousands except share data)	
Assets		
Current Assets		
Cash and cash equivalents	$ 14,603	$ 37,013
Marketable securities	52,336	55,971
Prepaid expenses and other current assets	1,768	2,110
Total current assets	68,707	95,094
Property and equipment, net	193	683
Other assets	983	979
Total assets	$ 69,883	$ 96,756
Liabilities and Stockholders Equity		
Current liabilities		
Accounts payable	$ 1,017	$ 1,166
Accrued expenses	4,033	5,534
Other current liabilities	1,695	1,700
Total current liabilities	6,745	8,400
Long-term liabilities	664	2,631
Total liabilities	7,409	11,031
Commitments and Contingencies (Note 14)		
Stockholders equity:		
Common stock, $0.01 par value; authorized 125,000,000 shares at December 31, 2017 and December 31, 2016; issued and outstanding 24,381,605 shares at December 31, 2017 and 24,359,584 shares at December 31, 2016	244	244
Preferred stock, $0.01 par value; authorized 5,000,000 shares; none outstanding		
Additional paid-in capital	267,642	264,017
Accumulated other comprehensive loss	(59)	(9)
Accumulated deficit	(205,353)	(178,527)
Total stockholders equity	62,474	85,725
Total liabilities and stockholders equity	$ 69,883	$ 96,756

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

	For the Years Ended December 31,		
	2017	2016	2015
	(in thousands except share and per share data)		
Operating expenses:			
General and administrative	$ 9,146	$ 21,815	$ 16,456
Research and development	17,948	31,317	18,991
Restructuring charges	1,038	8,179	
Total operating expenses	28,132	61,311	35,447
Loss from operations	(28,132)	(61,311)	(35,447)
Other expenses (income), net	(716)	(547)	300
Loss before income taxes	(27,416)	(60,764)	(35,747)
Provision (benefit) for income taxes	(590)	347	161
Net loss	(26,826)	(61,111)	(35,908)
Accretion of redeemable convertible preferred stock			(318)
Net loss attributable to common stockholders	$ (26,826)	$ (61,111)	$ (36,226)
Earnings per share attributable to common stockholders			
Basic	$ (1.10)	$ (2.51)	$ (3.25)
Diluted	$ (1.10)	$ (2.51)	$ (3.25)
Weighted-average shares outstanding:			
Basic	24,366,681	24,319,443	11,151,978
Diluted	24,366,681	24,319,443	11,151,978

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)

	For the Years Ended December 31,		
	2017	2016	2015
	(in thousands)		
Net loss	$ (26,826)	$ (61,111)	$ (35,908)
Other comprehensive income (loss):			
Unrealized gains (losses) on available for sale securities, net	(50)	(32)	23
Total other comprehensive income (loss)	(50)	(32)	23
Comprehensive loss	$ (26,876)	$ (61,143)	$ (35,885)

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

CONSOLIDATED STATEMENT OF REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS EQUITY (DEFICIT)

	Redeemable Convertible Preferred Stock										
	Series C Preferred		Series D Preferred		Series E Preferred		Total	Common Stock		Additional Paid-in	
mount	Shares	Amount	Shares	Amount	Shares	Amount	Amount	Shares	Amount	Capital	
					(in thousands except shares)						
9,144	40,430,250	$ 40,430	38,504,439	$ 22,054	33,774,763	$ 32,858	$ 104,486	44,326	$	$	9,490
											3,258
								205,721	2		682
								39,789	1		13
											63
					35,948,023	34,213	34,213				1,477
(9,144)	(40,430,250)	(40,430)	(38,504,439)	(22,054)	(69,722,786)	(67,389)	(139,017)	16,403,011	164		138,853
								7,319,750	73		106,451

		318	318			(318
$	$	$	$	24,012,597	$ 240	$ 259,969

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS EQUITY

	Common Stock Shares	Amount	Additional Paid-in Capital	Accumulated other comprehensive income	Accumulated Deficit	Total Stockholders Equity
			(in thousands except share data)			
Balance, December 31, 2015	24,012,597	$ 240	$ 259,969	$ 23	$ (117,416)	$ 142,816
Stock-based compensation			3,346			3,346
Exercise of stock options	292,235	3	597			600
Exercise of warrants into common stock	54,752	1	4			5
Additional paid in capital on account of vested portion of restricted stock			101			101
Other comprehensive loss				(32)		(32)
Net loss					(61,111)	(61,111)
Balance, December 31, 2016	24,359,584	244	264,017	(9)	(178,527)	85,725
Stock-based compensation			3,522			3,522
Exercise of stock options	22,021		2			2
Additional paid in capital on account of vested portion of restricted stock			101			101
Other comprehensive loss				(50)		(50)
Net loss					(26,826)	(26,826)
Balance, December 31, 2017	24,381,605	$ 244	$ 267,642	$ (59)	$ (205,353)	$ 62,474

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
Operating Activities:			
Net loss	$ (26,826)	$ (61,111)	$ (35,908)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	152	433	201
Stock-based compensation	3,522	3,346	3,258
Amortization of premium on marketable securities, net	(150)	(150)	46
Benefit for deferred income taxes	(884)	(16)	(30)
Non-cash interest expense	131	246	349
Non-cash restructuring charges		1,474	
Loss (gain) on sale of property and equipment		67	(5)
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	820	674	(1,737)
Accounts payable and accrued expenses	(1,616)	1,805	496
Other assets	402	(14)	(171)
Other current and long-term liabilities	25	1,282	198
Net cash used in operating activities	(24,424)	(51,964)	(33,303)
Investing Activities:			
Purchase of marketable securities	(89,163)	(117,146)	(108,236)
Maturities of marketable securities	92,898	169,006	500
Decrease in value of other assets			(1,119)
Purchases of property and equipment	(23)	(2,964)	(269)
Proceeds from sale of property and equipment		137	12
Net cash provided by (used in) investing activities	3,712	49,033	(109,112)
Financing Activities:			
Payment under license termination agreement	(1,700)	(1,700)	
Proceeds from issuance of Series E redeemable convertible preferred stock and warrants for common stock, net			35,690
Proceeds from the issuance of common stock, net			106,524
Proceeds from issuance of restricted stock			382
Exercise of warrants		5	14
Exercise of stock options	2	600	684
Net cash provided by (used in) financing activities	(1,698)	(1,095)	143,294
Net increase (decrease) in cash and cash equivalents	(22,410)	(4,026)	879
Cash and cash equivalents, beginning of year	37,013	41,039	40,160

Cash and cash equivalents, end of year	$ 14,603	$ 37,013	$ 41,039
Supplemental Non-Cash Financing Activities:			
Conversion of preferred stock	$	$	$ 139,017
Supplemental disclosures of cash flow information:			
Cash paid for income taxes	$ 51	$ 140	$ 69
Cash received for interest	$	$	$ 33

See accompanying notes to consolidated financial statements.

Table of Contents

CHIASMA, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of Business

Chiasma, Inc. is a clinical-stage biopharmaceutical company incorporated in 2001 under the laws of the State of Delaware. Chiasma, Inc. is headquartered in Massachusetts and has two wholly owned subsidiaries; Chiasma (Israel) Ltd., and Chiasma Securities Corp, collectively referred to as the Company, we, us, our or Chiasma. We are a clinical-stage biopharmaceutical company focused on improving the lives of patients who face challenges associated with their existing treatments for rare and serious chronic disease. Employing our proprietary Transient Permeability Enhancer (TPE) technology platform, we seek to develop oral medications that are currently available only as injections. We are currently developing oral octreotide capsules, conditionally trade-named MYCAPSSA, our sole TPE platform-based clinical product candidate, in two Phase 3 clinical trials in adult patients for the treatment of acromegaly to potentially support regulatory approval in the United States and Europe. Acromegaly is a rare and debilitating condition that results in the body s production of excess growth hormone. Octreotide is an analog of somatostatin, a natural inhibitor of growth hormone secretion. Octreotide capsules have been granted orphan designation in the United States and the European Union for the treatment of acromegaly. We retain worldwide rights to develop and commercialize octreotide capsules with no royalty obligations to third parties.

In September 2017, we initiated a third Phase 3 clinical trial for oral octreotide capsules for the maintenance therapy of adult patients with acromegaly following our agreement with the United States Food and Drug Administration (FDA) on the design of the trial, reached through a Special Protocol Assessment in August 2017. The trial, referred to as CHIASMA OPTIMAL, is a randomized, double-blind, placebo-controlled, nine-month trial expected to enroll 50 adult acromegaly patients designed to support regulatory approval of octreotide capsules in the United States. We are also currently conducting an international Phase 3 clinical trial, referred to as MPOWERED, of oral octreotide capsules for the maintenance treatment of adult patients with acromegaly to support regulatory approval in Europe. The MPOWERED trial is a global, randomized, open-label and active-controlled 15-month trial expected to enroll approximately 130 adult acromegaly patients, of which we expect to randomize at least 80 patients who are responders to octreotide capsules following a six-month run-in to either octreotide capsules or injectable somatostatin receptor ligands (octreotide or lanreotide), and then followed for an additional nine months.

2. Summary of Significant Accounting Policies

Principles of Consolidation and Basis of Presentation

The accompanying consolidated financial statements include the accounts of Chiasma, Inc. and its subsidiaries and are prepared in conformity with accounting principles generally accepted in the United States of America (U.S. GAAP) and are stated in U.S. dollars. The consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities in the ordinary course of business. All intercompany balances and transactions have been eliminated in consolidation.

On July 21, 2015, we completed the sale of 7,319,750 shares of our common stock in our IPO, at a price to the public of $16.00 per share, resulting in net proceeds to us of approximately $106.5 million after deducting underwriting discounts and commissions and offering expenses payable by us. In connection with the closing of the IPO on July 21, 2015, all of our outstanding redeemable convertible preferred stock automatically converted into 16,403,011 shares of common stock. The significant increase in shares outstanding in July 2015 impacted the year-over-year comparability of our net loss per share calculations for the year ended December 31, 2015.

Liquidity

We have incurred significant losses from operations since our inception and expect losses to continue for at least the next several years. We are heavily dependent on the regulatory approval and subsequent commercial success

Table of Contents

of our product candidate, octreotide capsules for the treatment of acromegaly in the United States and Europe, both of which may never occur.

We expect to continue with our ongoing international Phase 3 CHIASMA OPTIMAL clinical trial of octreotide capsules in acromegaly to support potential regulatory approval in the United States and ongoing international Phase 3 MPOWERED clinical trial of octreotide capsules in acromegaly to support potential regulatory approval in Europe. In June and August 2016, we announced two separate corporate restructuring plans, which were completed in 2017, intended to focus our resources on the continued development of octreotide capsules for the maintenance treatment of adult acromegaly patients. We currently expect our existing cash, cash equivalents and marketable securities to fund our operations for at least one year after the date these consolidated financial statements are issued. We expect to continue to incur significant operating losses for the foreseeable future.

Successful transition to attaining profitable operations is dependent upon achieving a level of revenues adequate to support our cost structure. We plan to continue to fund our losses from operations and capital funding needs from existing balances of cash, cash equivalents and marketable securities and potentially through the issuance of debt and/or equity or through collaborations or license agreements with other companies. Debt or equity financing may not be available on a timely basis on terms acceptable to us, or at all. If we are not able to secure adequate additional funding, we may be forced to make further reductions in spending, extend payment terms with suppliers, liquidate assets where possible, or suspend or curtail our planned development of octreotide capsules. Any of these actions could materially harm our business, results of operations and future prospects. Failure to obtain regulatory approval of octreotide capsules in acromegaly will prevent us from commercializing the product candidate, which could raise significant concerns about our continued viability as a business.

Use of estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. We base these estimates and assumptions on historical experience when available, and on various factors that we believe to be reasonable under the specific circumstances. Significant estimates relied upon in preparing the accompanying consolidated financial statements include, but are not limited to, the fair value of common stock and other equity instruments, accounting for stock-based compensation, present value of long-term purchase obligation, income taxes, and accounting for certain accruals. We assess these estimates on an ongoing basis; however, actual results could materially differ from those estimates.

Cash Equivalents

Cash and cash equivalents consist of highly liquid instruments which mature within three months or less from the date of purchase.

Marketable Securities

Our investments primarily consist of commercial paper and corporate and government debt securities. These marketable securities are classified as available-for-sale, and as such, are reported at fair value on our consolidated balance sheets. Unrealized holding gains and losses are reported within accumulated other comprehensive income as a separate component of stockholders equity. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization, together with interest on securities, are included in other expenses (income), net, on our consolidated statements of operations.

If a decline in the fair value of a marketable security below our cost basis is determined to be other than temporary, such marketable security is written down to its estimated fair value as a new cost basis and the amount of the write-down is included in earnings as an impairment charge. The cost of securities sold is based on the specific identification method.

Table of Contents

Foreign currency translation

We use the U.S. dollar as our functional currency. Monetary assets and liabilities denominated in foreign currency are re-measured at current rates and non-monetary assets denominated in foreign currency are recorded at historical exchange rates. Realized and unrealized exchange gains or losses from transactions and re-measurement adjustments are reflected in other expense (income), net, in the accompanying consolidated statements of operations.

Comprehensive income (loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Other than reported net income, comprehensive income (loss) includes unrealized gains and losses on available for sale securities, which are disclosed in the accompanying consolidated statements of comprehensive income. There were no reclassifications out of comprehensive income (loss) for the years ended December 31, 2017, 2016 or 2015.

Segment information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, our Chief Executive Officer, in making decisions regarding resource allocation and assessing performance. We view our operations and manage our business in one operating segment.

Other assets

Other assets consist of long-term restricted deposits, prepayments, and deferred tax assets. Long-term restricted deposits represent interest-bearing money market accounts held as security deposits against bank guarantees.

Concentrations of credit risk

Financial instruments that potentially subject us to significant concentration of credit risk consist primarily of cash, cash equivalents, and marketable securities. We routinely maintain deposits in financial institutions in excess of government insured limits. Management believes that we are not exposed to significant credit risk as our deposits are held at financial institutions that management believes to be of high credit quality and we have not experienced any significant losses in these deposits. We regularly invest excess operating cash in deposits with major financial institutions and money market funds and in notes issued by the U.S. government, as well as in fixed income investments and bond funds, both of which can be readily purchased and sold using established markets. We believe that the market risk arising from our holdings of these financial instruments is mitigated based on the fact that many of these securities are either government backed or of high credit rating.

Property and equipment

Property and equipment are stated at cost, net of accumulated depreciation and amortization. Expenditures for maintenance and repairs are charged to operations as incurred, whereas major betterments are capitalized as additions to property and equipment. Depreciation and amortization are recorded using the straight-line method over the estimated useful lives of the assets, as follows:

Asset Category	Estimated Useful Lives
Computer equipment and software	3 years
Office furniture and equipment	7 17 years (mainly 7)
Laboratory equipment	7 17 years (mainly 10)
Leasehold improvements	The lesser of lease term or estimated useful lives

Table of Contents

Impairment of long-lived assets

We review long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying amount of the asset may not be recoverable. When such events occur, we compare the carrying amounts of the assets to their undiscounted expected future cash flows the assets are expected to generate and to be recognized. The amount of impairment loss to be recognized is the excess of the carrying value over the fair value of the related asset. We did not record any impairments during the years ended December 31, 2017, 2016 (other than described in Note 17) and 2015.

Employment termination costs

We accrue employment termination liabilities when (a) management, having the authority to approve the action, commits to a plan of termination; (b) the plan identifies the number of employees to be terminated, their job classifications or functions, their locations, and the expected completion date; (c) the plan establishes the terms of the arrangement, including the benefits that employees will receive upon termination, in sufficient detail to enable employees to determine the type and amount of benefits they will receive upon involuntary termination; (d) it is unlikely that significant changes to the plan will be made or withdrawn; and (e) the plan has been communicated to the affected employees. When employees are required to render services beyond the minimum retention period through the involuntary termination date in order to receive the termination benefits, a liability is measured initially at the communication date based on the fair value of the liability, and is recognized ratably over the future service period through expected termination date. We reverse the liability when events or circumstances occur that discharge or remove its responsibility to settle the termination liability.

Long-term purchase obligation

Our long-term purchase obligation represents aggregate amounts payable to F. Hoffman- La Roche Ltd. and Hoffmann-La Roche Inc. (collectively Roche) for the purchase of certain active pharmaceutical ingredient (API) supplies and the trade name (MYCAPSSA) for octreotide capsules following the termination of our license agreement with Roche in July 2014. The amount is payable in three equal annual installments and is recorded at its present value. The difference between the aggregate purchase price and the present value of the installment payments represents the interest component of the financing arrangement and is recorded as interest expense over the payment term and included in other expenses (income), net, in the accompanying consolidated statements of operations.

Research and development

Research and development costs are expensed as incurred. Research and development costs include payroll and personnel expense, consulting costs, external contract research and development expenses, raw materials, drug product manufacturing costs, and allocated overhead including depreciation and amortization, rent, and utilities. Research and development costs that are paid in advance of performance are capitalized as a prepaid expense and amortized over the service period as the services are provided.

Clinical trial costs

Clinical trial costs are a component of research and development expenses. We accrue and expense clinical trial activities performed by third parties on an evaluation of the progress to completion of specific tasks using data such as hours spent in performance of services, patient enrollment, clinical site activation, and other information provided to us by our vendors. We make estimates of our clinical trial accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. If timelines or contracts are modified based upon

changes in the clinical trial protocol or scope of work to be performed, we assess our estimates of accrued expenses accordingly.

Table of Contents

Patent costs

Patent costs are expensed as incurred as their realization is uncertain. These costs are classified as general and administrative in the accompanying consolidated statements of operations.

Redeemable convertible preferred stock

We classify redeemable convertible preferred stock as temporary equity in the accompanying consolidated statement of redeemable convertible preferred stock and stockholders equity (deficit) due to redemption rights granted to the holders that are outside of our control. We recorded redeemable convertible stock initially at the original issuance price net of issuance costs and discounts, if any, according to relative fair value method. When the initial recorded amount is less than the redemption value, we accrete the recorded amount up to the redemption value over the redemption period using the effective interest method, plus dividends expected to be paid upon redemption, if any. We accrete the recorded amount up to the deemed liquidation upon the occurrence of any such event. On the effective date of our IPO, the redeemable convertible preferred stock automatically converted into common stock.

Warrants

Common stock warrants issued in connection with the issuance of redeemable convertible preferred stock were classified as a component of stockholders equity because they are free standing financial instruments that are legally detachable and separately exercisable from the redeemable convertible preferred stock, are contingently exercisable, do not embody an obligation for us to repurchase the shares, and permit the holders to receive a fixed number of common shares upon exercise. In addition, the common stock warrants require physical settlement and do not provide any guarantee of value or return. Common stock warrants were initially recorded at their relative fair value and were not subsequently re-measured. Common stock warrants were valued using Black-Scholes option pricing model.

Stock-based compensation

We account for all stock-based compensation to employees and nonemployees based on their fair values on the date of grant. The fair value of stock-based awards to nonemployees is remeasured as the award vests. For employee stock-based awards with only service conditions, we recognize compensation on a straight-line basis over the requisite service period, which is usually the vesting period of the award, net of any actual forfeitures.

We determine the fair value of stock options by using the Black-Scholes option pricing model. This model requires the input of several assumptions such as the expected option term, the expected risk-free interest rate over the expected option term, the expected volatility of our stock price over the expected option term, and the expected dividend yield over the expected option term. The computation of expected volatility is based on an average historical share price volatility based on an analysis of reported data for a peer group of comparable publicly traded companies, which were selected based upon industry similarities. The interest rate for periods within the expected term of the award is based on the U.S. Treasury risk-free interest rate in effect at the time of grant. The expected lives of the options were estimated using the simplified method. For options granted to non-employees, the expected life of the option used is the contractual term of each such option. All other assumptions used to calculate the grant date fair value are generally consistent with the assumptions used for options granted to employees. Stock-based compensation expense for awards granted to non-employees is adjusted as the award vests to reflect the current fair value of such awards, and is recognized using an accelerated attribution model.

Income taxes

The consolidated financial statements reflect provisions for federal, state, local and foreign income taxes. Deferred tax assets and liabilities represent future tax consequences of temporary differences between the

Table of Contents

financial statement carrying amounts and the tax basis of assets and liabilities and for loss carryforwards using enacted tax rates expected to be in effect in the years in which the differences reverse. A valuation allowance is recorded when it is more likely than not that some or all of the deferred tax assets will not be realized.

We determine whether it is more likely than not that a tax position will be sustained upon examination. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The tax benefit to be recognized for any tax position that meets the more likely than not recognition threshold is calculated as the largest amount that is more than 50% likely of being realized upon resolution of the contingency. We account for interest and penalties related to uncertain tax positions as part of our other expenses in the accompanying consolidated financial statements.

Contingent liabilities

In the normal course of business, we are subject to proceedings, lawsuits, and other claims and assessments. We assess the likelihood of any adverse judgments or outcomes to these matters as well as potential ranges of probable losses. A determination of the amount of reserves required, if any, for these contingencies is made after careful analysis of each individual issue. The required reserves may change in the future due to new developments in each matter or changes in approach such as a change in settlement strategy in dealing with these matters. We record charges for the losses we anticipate incurring in connection with litigation and claims against us when we conclude a loss is probable and we can reasonably estimate these losses.

Earnings per share attributable to common stockholders

We compute basic earnings per share attributable to common stockholders by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. During periods in which we incurred a net loss, we allocate no net loss to participating securities because they do not have a contractual obligation to share in the net loss. We compute diluted earnings per common share after giving consideration to all potentially dilutive common shares, including stock options, and warrants outstanding during the period except where the effect of such non-participating securities would be antidilutive.

Recently issued accounting pronouncements

In February 2016, the Financial Accounting Standards Board issued new guidance which establishes a right-of-use model that requires a lessee to record an asset and a lease liability on the balance sheet for all leases with terms longer than 12 months. Leases will be classified as either finance or operating, with classification affecting the pattern of expense recognition in the income statement. The new standard is effective for annual periods beginning after December 15, 2018, including interim periods within those annual reporting periods. A modified retrospective transition approach, which includes a number of optional practical expedients that we may elect to apply, is required for lessees for capital and operating leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements. We are currently evaluating the impact the standard may have on our consolidated financial statements and we currently expect that most of our operating lease commitments will be subject to the new standard and recognized as operating lease liabilities and right-of-use assets upon adoption.

Table of Contents

3. Investments

Our investments consisted of the following as of December 31, 2017 and 2016:

	As of December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	($ in thousands)			
Money market funds	$ 12,399	$	$	$ 12,399
Corporate notes	29,788		(35)	29,753
Commercial paper	22,607	1	(25)	22,583
Total	$ 64,794	$ 1	$ (60)	$ 64,735

	As of December 31, 2016			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	($ in thousands)			
Money market funds	$ 35,218	$	$	$ 35,218
Corporate notes	22,347		(7)	22,340
Commercial paper	33,633	7	(9)	33,631
Total	$ 91,198	$ 7	$ (16)	$ 91,189

As of December 31, 2017, we do not consider those securities that are in an unrealized loss position to be other-than-temporarily impaired, as we have the ability to hold such investments until recovery of the fair value. We utilize the specific identification method in computing realized gains and losses. We had no realized gains and losses on our available-for-sale securities for the years ended December 31, 2017, 2016 or 2015.

The fair values of our investments by classification in our consolidated balance sheets as of December 31, 2017 and 2016 were as follows:

	As of December 31,	
	2017	2016
	($ in thousands)	
Cash and cash equivalents	$ 12,399	$ 35,218
Marketable securities	52,336	55,971
Total	$ 64,735	$ 91,189

Cash and cash equivalents in the table above exclude cash of $2.2 million and $1.8 million as of December 31, 2017 and 2016, respectively. The contractual maturity dates of all of our investments are less than one year.

4. Fair Value Measurements and Fair Value of Financial Instruments

Certain assets and liabilities are reported at fair value on a recurring basis. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants at the measurement date. The fair value accounting guidance requires that assets and liabilities carried at fair value be classified and disclosed in one of the following three categories:

Level 1 Quoted prices in active markets for identical assets or liabilities that we have the ability to access at the measurement date.

Table of Contents

Level 2 Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3 Inputs that are unobservable for the asset or liability.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by us in determining fair value is greatest for instruments categorized in Level 3. A financial instrument s level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The following tables summarize the fair value measurements of our financial instruments as of December 31, 2017 and 2016:

	Fair Value Measurements at December 31, 2017			
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
		($ in thousands)		
Cash equivalents:				
Money market funds	$ 12,399	$	$	$ 12,399
Total cash equivalents	$ 12,399	$	$	$ 12,399
Marketable securities:				
Corporate notes	$	$ 29,753	$	$ 29,753
Commercial paper		22,583		22,583
Total marketable securities		52,336		52,336
Total	$ 12,399	$ 52,336	$	$ 64,735

	Fair Value Measurements at December 31, 2016			
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
		($ in thousands)		
Cash equivalents:				
Money market funds	$ 35,218	$	$	$ 35,218
Total cash equivalents	$ 35,218	$	$	$ 35,218

Marketable securities:			
Corporate notes	$	$ 22,340	$ 22,340
Commercial paper		33,631	33,631
Total marketable securities		55,971	55,971
Total	$ 35,218	$ 55,971	$ 91,189

Our cash equivalents are classified as Level 1 assets under the fair value hierarchy as these assets have been valued using quoted market prices in active markets and do not have any restrictions on redemption. Our marketable securities are classified as Level 2 assets under the fair value hierarchy as these assets were primarily determined from independent pricing services, which normally derive security prices from recently reported trades for identical or similar securities, making adjustments based upon other significant observable market transactions. At the end of each reporting period, we perform quantitative and qualitative analysis of prices received from third parties to determine whether prices are reasonable estimates of fair value. After completing our analysis, we did not adjust or override any fair value measurements provided by our pricing services as of December 31, 2017 or 2016. We did not have any Level 3 assets being measured at fair value on a recurring basis

Table of Contents

as of December 31, 2017 or 2016. There were no transfers between measurement levels during the years ended December 31, 2017 and 2016.

5. Earnings per Share Attributable to Common Stockholders

All common stock warrants and stock options have been excluded from the computation of diluted weighted-average shares outstanding because such securities would have an anti-dilutive impact due to net losses reported during the years ended December 31, 2017, 2016 and 2015. Since we have reported a net loss attributable to common stockholders for the years ended December 31, 2017, 2016 and 2015, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders for those periods.

6. Property and Equipment

Property and equipment consisted of the following as of December 31, 2017 and 2016:

	As of December 31,	
	2017	2016
	($ in thousands)	
Computer equipment and software	$ 359	$ 406
Office furniture and equipment	173	593
Property and equipment, at cost	532	999
Less accumulated depreciation	(339)	(316)
Property and equipment, net	$ 193	$ 683

Depreciation expense was $0.2 million, $0.4 million and $0.2 million for the years ended December 31, 2017, 2016 and 2015, respectively.

7. Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2017 and 2016:

	As of December 31,	
	2017	2016
	($ in thousands)	
Accrued general and administrative expenses	$ 752	$ 547
Accrued research and development expenses	2,501	2,107
Accrued payroll and employee benefits	780	2,597
Accrued restructuring costs		283
Total accrued expenses	$ 4,033	$ 5,534

8. License Agreement

In December 2012, we signed a license agreement with Roche, which was effective in January 2013, and granted Roche an exclusive, non-transferable license to our intellectual property related to the octreotide capsules. Under the terms of the agreement, Roche obtained worldwide rights to research, develop, make, import, export, sell, market or distribute the commercial product. We retained certain research and development activities under a joint development plan and all rights to the intellectual property contained in the agreement.

In July 2014, Roche terminated the license agreement. Upon termination, Roche returned all rights and documentation granted under the agreement to us. We were relieved of further obligations under the agreement.

Table of Contents

Following the termination of the license agreement, we are not entitled to further payments from Roche, Roche has no remaining rights to octreotide capsules and we retain all rights to octreotide capsules and all related intellectual property. Subsequent to the termination, we purchased from Roche API supplies to continue the development and manufacturing of octreotide capsules as well as Roche s proposed trade name for octreotide capsules for an aggregate amount of $5.1 million payable in three equal annual installments of $1.7 million beginning in 2016. We made the $1.7 million annual payments in March of 2018, 2017, and 2016. The difference between the aggregate purchase price and the present value of the installment payments represents the interest component of the financing arrangement and is being recorded as interest expense over the payment term. Other than these payments, we have no other financial and operational obligations to Roche.

9. Warrants

As of December 31, 2015, there were warrants outstanding for the purchase of 3,621,767 shares of common stock with exercise prices ranging from $0.09 to $9.13. The warrants were issued at various points between June 2011 and February 2015 with expiration dates ranging from June 2016 through February 2025. There were no warrants exercised during the year ended December 31, 2017. There were 54,752 warrants exercised during the year ended December 31, 2016. There were warrants for the purchase of 3,567,015 shares of common stock outstanding as of December 31, 2017.

10. Redeemable Convertible Preferred Stock

During the years ended December 2012 and 2013, we issued an aggregate of 38,504,439 shares of Series D redeemable convertible preferred stock (the Series D preferred) and warrants to purchase up to an aggregate of 1,698,066 shares of Common Stock at an exercise price of $0.09 per share (the Warrants), for aggregate gross proceeds of $38.5 million, of which $34.8 million was allocated to the Series D preferred and $3.6 million was allocated to the Warrants, net of issuance cost in the amount of $0.1 million. Since the Series D preferred was issued in conjunction with freestanding detachable warrants, the proceeds from the issuance were allocated to each freestanding instrument based on their relative fair value.

We accreted the discount amount due to the Warrants allocation and issuance cost, using the interest method, until August 2014 which was the earliest redemption date of the instrument according to our certificate of incorporation then in effect.

In March 2013, we redeemed our Series B1 redeemable convertible preferred stock (Series B1 preferred), Series C preferred, and Series D preferred (collectively, the Original Preferred Stock) using proceeds received from the license agreement with Roche (see Note 8), which redemption was effected in accordance with the deemed liquidation provisions of our certificate of incorporation then in effect. Pursuant to such deemed liquidation provisions, upon such an event the Series D preferred was entitled to a redemption amount equal to its original issuance price plus $38.5 million. Accordingly, we immediately recognized the change in the redemption value in the amount of $38.5 million against accumulated deficit. The consideration for the redemption consisted of a cash payment of $55.0 million and the issuance of 1,134,997 shares of Series B1 redeemable convertible preferred stock (Series B1 preferred), 40,430,250 shares of Series C redeemable convertible preferred stock (Series C preferred), and 38,504,439 shares of Series D redeemable convertible preferred stock (Series D preferred , and collectively with the Series B1 preferred and Series C preferred, the Prime Preferred Stock). The Prime Preferred Stock bears similar terms, rights and preferences as the Original Preferred Stock, other than changes to reflect redemption payment of Series D preferred described above. In addition, the holders of the Original Preferred Stock received rights to receive future contingent payments under the Roche license agreement. Upon termination of the license agreement, these rights were also terminated.

The initial carrying value of the Prime Preferred Stock equaled the carrying value of the Original Preferred Stock on the redemption date. We accreted the carrying value of the Series D preferred to its redemption value until August 2014, which was the earliest redemption date of the Series D preferred according to our certificate of incorporation.

Table of Contents

In December 2014, we issued 33,774,763 shares of Series E redeemable convertible preferred stock (Series E preferred) at $1.00 per share, resulting in gross proceeds of $33.8 million, with issuance costs of $0.2 million. In connection with the issuance of Series E preferred, we issued to the holders warrants to purchase 924,622 shares of our common stock with an exercise price of $9.13 per share and allocated $0.8 million of the net proceeds to the warrants based on their relative fair value on the issuance date which was accounted for as a discount on Series E preferred and recorded as additional paid-in capital.

In February 2015, we increased the number of authorized shares of Series E redeemable convertible preferred stock (Series E preferred) to a total of 80,774,458 shares and subsequently sold and issued an aggregate of 35,948,023 shares of Series E preferred at $1.00 per share for gross proceeds of $35.9 million, with of issuance costs of $0.3 million. In connection with the issuance of Series E preferred, we issued to the holders of Series E preferred warrants to purchase 984,116 shares of our common stock, with an exercise price of $9.13 per share and allocated $1.5 million of the net proceeds to the warrants based on their relative fair value on the issuance date which was accounted for as a discount on Series E preferred and recorded as additional paid in capital.

In connection with the closing of the IPO on July 21, 2015, all of the outstanding redeemable convertible preferred stock automatically converted into 16,403,011 shares of common stock.

11. Common Stock

On July 21, 2015, we issued 7,319,750 shares of our common stock, $0.01 par value per share, at a price to the public of $16.00 per share before underwriting discounts. We raised approximately $106.5 million in net proceeds after deducting underwriting discounts and commissions and offering expenses.

12. Stock Incentive Plan

In 2008, our Board of Directors adopted the 2008 Stock Incentive Plan (the 2008 Plan), which provided for the grant of incentive stock options, nonqualified stock options, and restricted stock to our employees, directors, and nonemployees up to 3,547,741 shares of common stock. Option awards expire 10 years from the grant date and generally vest over four years, but vesting conditions can vary at the discretion of our Board of Directors.

In July 2015, we approved a 2015 Stock Option and Incentive Plan (the 2015 Plan), which became effective upon our IPO. The 2015 Plan allows the grant of incentive stock options, nonqualified stock options, and restricted stock to employees, directors, and nonemployees of Chiasma up to 3,566,296 shares of common stock. In connection with the adoption of the 2015 Plan, no further option grants are permitted under the 2008 Plan and any expirations, cancellations, or terminations under the previous plan are available for issuance under the 2015 Plan. On January 1, 2016, the number of shares reserved and available for issuance under the 2015 Stock Plan increased by 960,504 shares of common stock pursuant to a provision in the 2015 Stock Plan that provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2016, by 4% of the number of shares of common stock issued and outstanding on the immediately preceding December 31 or such lesser number as determined by the compensation committee of the Board of Directors. The compensation committee of the Board of Directors determined there would be no increase to the shares reserved and available under the 2015 Stock Plan on January 1, 2018 and 2017. As of December 31, 2017, the total number of shares authorized for stock award plans is 7,114,037 of which 3,190,015 remain available for grant. There are 3,609,766 stock options outstanding as of December 31, 2017. The fair value of each stock option issued was estimated at the date of grant using the following weighted-average assumptions:

	For the Years Ended December 31,		
	2017	**2016**	**2015**
Expected volatility	74%	75%	75%
Expected term (years)	5.69	6.22	6.26
Risk-free interest rate	1.81%	1.45%	1.71%
Expected dividend yield	0%	0%	0%

Table of Contents

A summary of option activity as of December 31, 2017 and the year then ended is presented below:

	Number of Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding, January 1, 2017	3,652,801	$ 4.95	8.27	$ 779,340
Exercised	(22,021)	$ 0.09		
Granted	116,750	$ 1.48		
Forfeited/Expired	(137,764)	$ 9.18		
Outstanding, December 31, 2017	3,609,766	$ 4.71	7.38	$ 668,434
Exercisable, December 31, 2017	2,250,316	$ 4.68	6.80	$ 632,034
Vested and expected to vest, December 31, 2017	3,609,766	$ 4.71	$ 7.38	$ 668,434

The weighted-average grant date per-share fair value of stock options granted during 2017, 2016 and 2015 was $0.95, $4.38 and $6.76, respectively. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2017, 2016 and 2015 was approximately $40,000, $3.5 million and $1.8 million, respectively.

At December 31, 2017, there was $4.1 million of unrecognized compensation cost related to stock options, which is expected to be recognized over a weighted-average period of 2.0 years.

Stock-based compensation expense for 2017, 2016 and 2015 consisted of the following:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
General and administrative	$ 1,510	$ 1,717	$ 1,848
Research and development	2,012	1,629	1,410
Total	$ 3,522	$ 3,346	$ 3,258

During 2015, two directors exercised options to purchase an aggregate of 122,644 shares of common stock of which 116,258 of the shares were issued as restricted stock as they were exercised prior to full vesting. The proceeds from the issuance of the restricted stock are presented as long-term liabilities within the accompanying consolidated balance sheet, since we have the right to repurchase the unvested portion of the restricted stock following termination of the services of their holder. The long-term liability is released to additional paid-in capital per the original vesting schedule of the options. As of December 31, 2017, there were 35,772 restricted shares outstanding and the outstanding balance of the liability was $0.1 million. The weighted average grant date fair value of the options was $2.62.

Table of Contents

13. Income Taxes

Our loss before provision for income taxes for the years ended December 31, 2017, 2016 and 2015 consisted of the following:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
Domestic	$ (27,703)	$ (61,390)	$ (35,219)
Foreign	287	626	(528)
Total	$ (27,416)	$ (60,764)	$ (35,747)

The components of income tax provision (benefit) consisted of the following for the years ended December 31, 2017, 2016 and 2015:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
Current provision for income taxes:			
U.S.	$ 13	$ 12	$
Foreign	281	351	191
Total current provision for income taxes	294	363	191
Deferred tax benefit - U.S. Federal	(956)		
Deferred tax provision (benefit) - foreign	72	(16)	(30)
Total deferred benefit for income taxes	(884)	(16)	(30)
Total provision (benefit) for income taxes	$ (590)	$ 347	$ 161

A reconciliation setting forth the differences between our effective tax rates and the U.S. federal statutory tax rate is as follows:

	For the Years Ended December 31,		
	2017	2016	2015
U.S. federal tax provision at statutory rate	34.00%	34.00%	34.00%
State and local tax, net of federal benefit	4.39%	4.75%	5.64%
Foreign rate differences	0.79%	0.42%	0.08%
Non-deductible foreign stock compensation	(1.73%)	(0.63%)	(1.16%)

Effect of other permanent differences	(0.66%)	(0.29%)	(0.05%)
Uncertain tax positions	0.13%	(0.03%)	(0.53%)
Change in valuation allowance	33.17%	(39.99%)	(37.74%)
Federal Tax Reform Rate Change	(68.55%)	0.00%	0.00%
Other adjustments	0.62%	1.16%	(0.69%)
Effective tax rate	2.16%	(0.61%)	(0.45%)

Table of Contents

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income and for tax carryforwards. Significant components of our deferred tax assets and liabilities as of December 31, 2017 and 2016 are as follows:

	As of December 31,	
	2017	2016
	($ in thousands)	
Deferred tax assets:		
Federal and state net operating loss carryforwards	$ 37,882	$ 44,778
Tax credit carryforwards		1,024
Intangible and other related assets	312	347
Accrued expenses	627	1,826
Stock compensation	1,067	979
Other	120	251
Total deferred tax assets	40,008	49,205
Valuation allowance	(39,984)	(49,119)
Net deferred tax assets	$ 24	$ 86

When realization of a deferred tax asset is more likely than not to occur, the benefit related to the deductible temporary differences attributable to operations is recognized as a reduction of income tax expense. Valuation allowances are provided against deferred tax assets when, based on all available evidence, it is considered more likely than not that some portion or all of the recorded deferred tax assets will not be realized in future periods. We cannot be certain that future U.S. taxable income will be sufficient to realize our deferred tax assets. Accordingly, a full valuation allowance has been provided against our U.S. net deferred tax assets. The valuation allowance decreased by $9.1 million and increased by $24.3 million in 2017 and 2016, respectively. The decrease in 2017 is primarily related to Federal tax reform reducing the Federal tax rate to 21% which resulted in a decrease to our deferred assets and a corresponding decrease to the valuation allowance. The increase in 2016 is primarily the result of an increase in net operating loss (NOL) carryforwards.

In December 2017, the Tax Cuts and Jobs Act of 2017 (tax reform or the tax law) was enacted. The tax reform reduced our U.S. corporate income tax rate from 34% to 21% beginning in 2018. Deferred tax assets and liabilities are measured using the enacted rate for the period in which they are expected to reverse. Accordingly, the reduction to the U.S. Federal corporate tax rate reduced our net U.S. deferred tax asset by $18.8 million which was offset by a corresponding reduction to its valuation allowance. In addition, the tax reform includes a transition tax in which all foreign earnings are deemed to be repatriated to the U.S. We are in the process of calculating the impact of the transition tax. Pursuant to Staff Accounting Bulletin No. 118, our measurement period for the tax impact of the transition tax is still open. At this time, we do not anticipate future material adjustments to our financial statements due to the transition tax.

At December 31, 2017, we had U.S. Federal and state NOL carryforwards totaling approximately $146.4 million and $113.1 million, respectively, that expire at various dates through 2037. At December 31, 2017, we had no Israeli NOL carryforwards, and approximately $1.0 million of U.S. Federal alternative minimum tax credit carryforwards that do not expire. The tax reform also allows us to receive the U.S. Federal alternative minimum tax credit carryforward in the form of a refund from 2018 through 2021. We have a history of generating losses and are forecasting that we will

not generate taxable income through 2021 which would otherwise limit our ability to realize the U.S. Federal alternative minimum tax credit. Accordingly, we have recorded a receivable of $1.0 million for the U.S. Federal alternative minimum tax credit refund in the accompanying consolidated balance sheet as of December 31, 2017.

Under Section 382 of the Internal Revenue Code of 1986, as amended, substantial changes in our ownership may limit the amount of NOL carryforwards that can be utilized annually in the future to offset our U.S. Federal

Table of Contents

taxable income. Specifically, this limitation may arise in the event of a cumulative change in our ownership of more than 50% within any three-year period. We have determined that we experienced an ownership change for purposes of Section 382 in August 2005 and May 2008. These ownership changes resulted in annual limitations to the amount of NOL carryforwards that can be utilized to offset future taxable income, if any, at the U.S. Federal level. The annual limit is approximately $0.1 million for 2008, and each year thereafter. We are currently in the process of performing a Section 382 study for our year ended December 31, 2017. At this point in time, it is uncertain if we have undergone an ownership change as defined by Section 382. If we have in fact undergone an ownership change, our NOL carryforwards may be substantially limited.

Our Israeli subsidiary has been recognized as a research and development company by the Head of the Israeli Administration of Industrial Research and Development and is entitled to tax benefits by virtue of the beneficiary enterprise status granted to part of its business activities under the Israeli Law for the Encouragement of Capital Investments 1959. The tax benefits include reduced tax rates on the research and development portion of its income during the first ten years of the benefit period (commenced in 2008). We benefit from a 20.6% tax rate for its income derived from research and development activities. Our tax rate on income from non-research and development activities is 24.0%. The continued application of the tax benefits is subject to certain conditions as defined by Israeli law.

As part of the transition tax provision, we have a deemed repatriation of all of our undistributed earnings as of December 31, 2017. However, our subsidiary s earnings, if distributed, would still be subject to local withholding tax and state income taxes. The subsidiary has undistributed earnings of approximately $2.3 million as of December 31, 2017, which is considered to be permanently reinvested in the operations of the subsidiary. If the earnings were to be distributed to the U.S. parent, they would be subject to Israeli withholding and state income tax liabilities. The unrecognized deferred tax liability is approximately $0.3 million.

We file U.S. federal, various state and Israeli income tax returns. The associated tax filings remain subject to examination by applicable tax authorities for a certain length of time following the tax year to which those filings relate. As we are in a loss carry-forward position, we are generally subject to U.S. Federal and state examinations for all years for which the Company generated losses that are included in the available losses carried forward to the current period. As of December 31, 2017, a summary of the tax years that remain subject to examination in our taxing jurisdictions is as follows:

United States	2003 and forward
Israel	2013 and forward

We have reviewed the tax positions taken, or to be taken, in our tax returns for all tax years currently open to examination by a taxing authority. We have recorded minimal interest or penalties related to uncertain tax positions. We remain subject to examination until the statute of limitations expires for each respective tax jurisdiction. The statute of limitations will be open with respect to these tax positions until 2021. A reconciliation of the beginning and ending amount of our unrecognized tax benefits is as follows:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		

Uncertain tax position at the beginning of year	$ 460	$ 429	$ 241
Additions for uncertain tax positions of prior year	45		
Additions for uncertain tax positions of current year		40	188
Reductions for settlements with taxing authorities			
Reductions for lapses of the applicable statutes of limitations	(34)	(9)	
Uncertain tax position at the end of the year	$ 471	$ 460	$ 429

Table of Contents

14. Commitments and Contingencies

We conduct certain of our operations in leased facilities, which are accounted for as operating leases. Certain leases include renewal options. In addition, we lease automobiles and equipment under operating leases. There were no assets held under capital leases at December 31, 2017 and 2016. Rent expense was as follows for 2017, 2016 and 2015:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
Rent Expense	$ 945	$ 1,221	$ 347

At December 31, 2017, the minimum rental commitments under all non-cancelable operating leases with initial or remaining terms of more than one year, for each of the following fiscal years, are as follows:

	For the Years Ended December 31,					
	2018	2019	2020	2021	2022	Thereafter
	($ in thousands)					
Operating Leases	$ 156	$ 110	$ 104	$	$	$

Legal Proceedings

On June 9, 2016, Chiasma, Inc. and certain of our current and former officers were named as defendants in a purported federal securities class action lawsuit filed in the United States District Court for the District of Massachusetts, styled *Gerneth v. Chiasma, Inc., et al*. This lawsuit challenges our public statements regarding our Phase 3 clinical trial methodology for octreotide capsules and our ability to obtain FDA approval for the marketing and sale of octreotide capsules. In December 2016, a lead plaintiff was appointed in the case. An amended complaint was filed by the lead plaintiff on February 10, 2017 similarly challenging our statements regarding the Phase 3 clinical trial methodology and results, and our ability to obtain FDA approval for octreotide capsules, in violation of Sections 11 and 15 of the Securities Act of 1933. The amended complaint adds as defendants current and former members of our board of directors, as well as the investment banks that underwrote our initial public offering (IPO) on July 15, 2015. The lead plaintiff seeks to represent a class of all purchasers of our stock in our IPO. The plaintiff is seeking an unspecified amount of compensatory damages on behalf of himself and members of a putative shareholder class, including interest and reasonable costs and expenses incurred in litigating the action, and any other relief the court determines is appropriate. The defendants filed a motion to dismiss the amended complaint on March 27, 2017 and on February 15, 2018, the court denied defendants motion to dismiss. We believe this lawsuit is meritless and intend to vigorously defend against it. At this time, no assessment can be made as to the likely outcome of this lawsuit or whether the outcome will be material to us.

15. Related Party Transactions

In August 2014, we signed a consulting agreement, which was amended in January 2016 and December 2016, with one of our investors and a representative of this investor to serve as our head of clinical. Costs incurred for services rendered by the head of clinical were $0.2 million, $0.5 million and $0.4 million for the years ended December 31, 2017, 2016 and 2015, respectively. Related to this consulting agreement, there were $0.1 million and $0.2 million of

accrued liabilities as of December 31, 2017 and 2016, respectively, recorded in our consolidated balance sheets.

In December 2014, we entered into a consulting agreement with a representative of another investor to provide financial and strategic consulting services to us. This agreement was terminated in March 2016. During the years ended December 31, 2016 and 2015, we recorded $0.2 million and $0.9 million, respectively, of expense related to this agreement, and which were classified as general and administrative expenses in the accompanying consolidated statements of operations.

Table of Contents

16. Employee Benefit Plans

Pursuant to the Israeli Severance Pay Law 1963, Israeli employees are entitled to severance pay equal to one month s salary for each year of employment, or a portion thereof. The employees of Chiasma (Israel) Ltd. are included under Section 14 of the Severance Pay Law, under which these employees are entitled to monthly deposits, which relieve us from future obligations under this law. As a result, no assets or liabilities are recorded in the accompanying consolidated balance sheets. In addition, we make mandated monthly contributions to an Israeli government retirement benefit plan for our Israeli employees. Beginning in 2016, we provide a 401(k) profit-sharing plan covering eligible U.S. employees to make tax deferred contributions, a portion of which are matched by us. All matching contributions and participant contributions vest immediately. During the years ended December 31, 2017, 2016 and 2015, we recorded expenses of $0.2 million, $0.5 million and $0.1 million, respectively related to these employee benefit plans.

17. Restructuring Charges

In November 2017, we finalized the termination of our lease agreement on our 24,000 square foot office facility in Waltham, MA which we no longer required following the 2016 workforce reductions. As a result, we recorded approximately $1.0 million of restructuring expenses during the year ended December 31, 2017, which consisted of a lease termination payment of $1.0 million, the write-off of office furniture and equipment of $0.4 million offset by the release of deferred rent liabilities of $0.4 million associated with the terminated lease.

In June 2016, we announced a corporate restructuring plan, including an immediate reduction of approximately 33% of our workforce, including substantially all of our commercial personnel. In August 2016, we announced a second corporate restructuring plan, including an immediate reduction of approximately 44% of our remaining workforce. In aggregate, these restructuring plans resulted in a reduction to our workforce of more than 60% since May 1, 2016. As a result of the August reduction in force, we no longer required the research lab and additional office space of the Israel facility and we were able to early terminate the Israel lease in November 2016. Accordingly, we recorded restructuring charges totaling $8.2 million during the year ended December 31, 2016 which consisted of employee severance benefits and related costs of $2.2 million, manufacturing commitment-related suspension fees of $4.5 million, non-cash restructuring charges of $0.8 million resulting from the impairment of leasehold improvements of $1.7 million offset by the forgiveness of tenant allowances received under the lease of $0.9 million and non-cash restructuring charges related to the impairment of previously capitalized commercial software and laboratory equipment of $0.7 million.

The components of our restructuring charges are as follows:

	2017	2016
	($ in thousands)	
Severance benefits and related costs	$	$ 2,211
Lease termination fees	1,038	
Non-cash restructuring charges		1,474
Manufacturing suspension fees		4,494
Total	$ 1,038	$ 8,179

Table of Contents

Activity related to accrued restructuring costs is as follows:

	2017	2016
	($ in thousands)	
Balance at beginning of year	$ 283	$
Plus:		
Current year restructuring costs	1,038	8,179
Less:		
Lease termination costs	1,038	
Payment of employee severance costs	283	1,928
Payment of manufacturing suspension fees		4,494
Non-cash restructuring charges		1,474
Balance at end of year	$	$ 283

18. Other Expenses (Income), net

Other expenses (income), net are as follows:

	For the Years Ended December 31,		
	2017	2016	2015
	($ in thousands)		
Loss / (Gain) on foreign currency transactions, net	$ 81	$ (9)	$
Interest income	(928)	(802)	(128)
Interest expense	131	264	349
Other expenses			79
Total	$ (716)	$ (547)	$ 300

19. Quarterly Financial Data (unaudited)

	Three Months Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	($ in thousands, except for per share data)			
Loss from operations	$ (7,115)	$ (6,920)	$ (6,943)	$ (7,154)
Net loss	(7,020)	(6,854)	(6,849)	(6,103)
Net loss attributable to common stockholders	(7,020)	(6,854)	(6,849)	(6,103)
Earnings per share attributed to common stockholders -				

Basic	$ (0.29)	$ (0.28)	$ (0.28)	$ (0.25)
Diluted	$ (0.29)	$ (0.28)	$ (0.28)	$ (0.25)

	Three Months Ended			
	March 31, 2016	**June 30, 2016**	**September 30, 2016**	**December 31, 2016**
	($ in thousands, except for per share data)			
Loss from operations	$ (17,220)	$ (26,708)	$ (9,439)	$ (7,944)
Net loss	(17,180)	(26,663)	(9,373)	(7,895)
Net loss attributable to common stockholders	(17,180)	(26,663)	(9,373)	(7,895)
Earnings per share attributed to common stockholders -				
Basic	$ (0.71)	$ (1.10)	$ (0.38)	$ (0.32)
Diluted	$ (0.71)	$ (1.10)	$ (0.38)	$ (0.32)