UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 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, 2019

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 001-38584

CONSTELLATION PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**26-1741721**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
215 First Street, Suite 200 Cambridge, Massachusetts	**02142**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 714-0555

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

Title of Class	**Trading symbol(s)**	**Name of Exchange on Which Registered**
Common Stock, $0.0001 par value per share	**CNST**	**Nasdaq Global Select 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 15(d) of the 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 every Interactive Data File required to be submitted 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 such files). YES ☒ NO ☐

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.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	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 ☒

As of June 30, 2019, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $177.0 million.

The number of shares of Registrant's Common Stock outstanding as of March 6, 2020 was 41,812,297.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A relating to the 2020 Annual Meeting of Stockholders within 120 days of the end of the registrant's fiscal year ended December 31, 2019. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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References to Constellation

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

Special Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K contains forward-looking statements regarding, among other things, our future discovery and development efforts, our future operating results and financial position, our business strategy, and other objectives for our operations. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our ongoing clinical trials, including our Phase 2 clinical trial of CPI-0610, our Phase 1b/2 clinical trial of CPI-1205 and our Phase 1/2 clinical trial of CPI-0209;
- our plans to advance our clinical-stage product candidates into later stage trials, including our plans to conduct a Phase 3 trial of CPI-0610
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our plans to develop and, if approved, subsequently commercialize CPI-0610, CPI-1205, CPI-0209 and any other product candidates, including in combination with other drugs and therapies;
- the timing of and our ability to submit applications for, obtain and maintain regulatory approvals for CPI-0610, CPI-1205, CPI-0209 and other product candidates;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash, cash equivalents and marketable securities;
- the potential advantages of our product candidates;
- our estimates regarding the potential market opportunity for our product candidates;
- our manufacturing, commercialization and marketing capabilities and strategy;
- our intellectual property position;
- our ability to identify products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- our estimates regarding expenses, future revenue, timing of any future revenue, capital requirements and needs for additional financing;
- the impact of government laws and regulations;
- our competitive position;
- developments relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding; and
- our expectations regarding the time during which we will be an emerging growth company or smaller reporting company as defined in federal securities laws and regulations.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the section entitled “Risk Factors” in Part I that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This Annual Report on Form 10-K includes statistical and other industry and market data, which we obtained from our own internal estimates and research, as well as from industry and general publications and research, surveys, and studies conducted by third parties. Industry publications, studies, and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

PART I

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company using our expertise in epigenetics to discover and develop novel therapeutics that address serious unmet medical needs in patients with cancers associated with abnormal gene expression or drug resistance. Our integrated epigenetics platform enables us to validate targets and generate small molecules impacting these targets to selectively modulate gene expression in tumor and immune cells to drive anti-tumor activity. This platform reflects our deep understanding of the biology of regulation of gene expression by epigenetic regulatory proteins, or epigenetic regulators, the development of small-molecule product candidates that selectively modulate their activity, and the design of clinical development programs supported by novel biomarker strategies. We are able to target a broad variety of epigenetic regulators using our platform and have generated development candidates acting against distinct classes of those regulators. Our vision is to become a fully integrated oncology company, with broad-based capabilities from target identification and compound discovery to clinical development and commercialization.

We have utilized our epigenetics platform to discover and design our wholly owned product candidates CPI-0610, CPI-1205, and CPI-0209. We continue to leverage this platform and our clinical experience to develop these product candidates and to discover and develop additional product candidates. CPI-0610 inhibits bromodomain and extra terminal domain, or BET, proteins. CPI-1205 and CPI-0209 inhibit the enhancer of zeste homolog 2, or EZH2, protein. We believe that our approach to targeting these central gene regulatory mechanisms associated with cancer proliferation may enable us to provide therapeutic benefits to cancer patients.

We have observed preliminary evidence of clinical activity in patients with myelofibrosis, or MF, treated with CPI-0610 in MANIFEST, an ongoing open-label Phase 2 clinical trial of CPI-0610 as a monotherapy and in combination with ruxolitinib (marketed as Jakafi®/Jakavi®). At the American Society of Hematology, or ASH, annual meeting in December 2019, we presented preliminary data that showed signs of activity for CPI-0610 across a broad range of parameters as both a first-line and second-line treatment for patients with MF, suggesting that CPI-0610 may have possible disease-modifying effects. See the section below titled *Our Product Candidates/CPI-0610—BET Inhibitor/Clinical Development* for more information. We are currently planning to advance CPI-0610 into a Phase 3 clinical trial in the third quarter of 2020, after consultation with the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA.

We have also observed preliminary evidence of clinical activity in patients with metastatic castration-resistant prostate cancer, or mCRPC, treated in ProSTAR, an ongoing open-label Phase 1b/2 clinical trial of CPI-1205 in combination with androgen receptor signaling, or ARS, inhibitors. At the American Association for Cancer Research meeting in April 2019, we presented preliminary data showing evidence of deep and durable effects in certain subsets of mCRPC patients in the Phase 1b portion of ProSTAR. We aim to gather additional clinical data, including data on durability of effect and on biomarkers that may identify target patient populations likely to benefit from treatment with CPI-1205, in order to make a decision about the further development of the compound in mid-2020, including whether to initiate a Phase 3 clinical trial. A clear signal is required to move the program into Phase 3. See the section below titled *Our Product Candidates/CPI-1205—EZH2 Inhibitor/Clinical Development* for more information.

We are currently conducting the Phase 1 portion of a Phase 1/2 clinical trial of CPI-0209, our second-generation EZH2 inhibitor. Based on preclinical data, we believe the compound could achieve more comprehensive coverage of EZH2 than first-generation EZH2 inhibitors and address additional patient populations beyond those that have been targeted by first-generation EZH2 inhibitors. We aim to determine the recommended Phase 2 dose for CPI-0209 during 2020.

BET Inhibitor

CPI-0610 is a small molecule designed to promote anti-tumor activity by specifically inhibiting the function of BET proteins, which normally enhance target gene expression. We are currently conducting MANIFEST, a Phase 2 clinical trial of CPI-0610 as a monotherapy and in combination with ruxolitinib (marketed as Jakafi®/Jakavi®) in patients with MF. The FDA granted orphan drug designation to CPI-0610 for the treatment of MF on November 20, 2019.

We are enrolling MF patients who are Janus-kinase-1/2, or JAK1/JAK2-, inhibitor-naïve, a first-line, or 1L, setting, as well as patients who are refractory to or intolerant of, or have had a sub-optimal response to, ruxolitinib, a second-line, or 2L, setting. In the 1L setting, we are testing CPI-0610 in combination with ruxolitinib in JAK1/JAK2-inhibitor-naïve patients with the aim of measuring spleen volume reduction and symptom improvement, among other relevant parameters. In the 2L setting, we are stratifying patients for dependence on red-blood-cell, or RBC, transfusions. In transfusion-dependent, or TD, patients, we are measuring conversion to transfusion independence, or TI, in addition to spleen volume reduction and symptom improvement. In non-TD patients, we are measuring spleen volume reduction and symptom improvement, among other parameters.

We believe there is a significant opportunity to improve treatment of MF patients. Ruxolitinib and fedratinib (marketed as Inrebic®) are the two approved drug therapies for MF in the United States, and ruxolitinib is the worldwide standard of care for the disease. In clinical trials, ruxolitinib has been shown to reduce spleen volume and improve patient-reported symptoms in a minority of patients. However, ruxolitinib has been associated with worsening hematological parameters, including thrombocytopenia, anemia, and transfusion dependence. The product also has demonstrated a limited ability to improve bone marrow fibrosis, which has been documented as a primary cause of morbidity and mortality in MF. Some patients cannot start treatment with ruxolitinib, in some cases because of low platelet levels, low hemoglobin levels, or RBC transfusion dependence. Other patients treated with ruxolitinib do not achieve targeted clinical outcomes, such as a 35% or greater reduction in spleen volume or a 50% improvement in symptom scores. Approximately three-quarters of patients in clinical trials discontinued use of ruxolitinib within five years, in part due to side effects or relapse / recurrence of their disease.

We believe that preliminary data from MANIFEST suggest that CPI-0610 has the potential to offer meaningful benefits beyond the current standard of care in MF. We have observed preliminary evidence of activity of CPI-0610 as a monotherapy and in combination with ruxolitinib across a range of parameters in MF, including reduction in spleen volume as measured by magnetic resonance imaging, or MRI; improvements in patient-reported symptoms; improvements in anemia and conversion from transfusion dependence to transfusion independence; and improvements in bone marrow fibrosis. While these preliminary data need to be confirmed in a larger dataset, we believe that these data suggest that CPI-0610 may have disease-modifying effects. We believe that evidence of hemoglobin improvement with CPI-0610 may provide a benefit to patients with anemia, which is associated with both myelofibrosis itself and with treatment by ruxolitinib. See the section below titled *Our Product Candidates/CPI-0610—BET Inhibitor/Clinical Development* for more information.

In addition to the activity of CPI-0610, we believe that the compound may have a differentiated safety profile compared with some other BET inhibitors. Clinical testing of CPI-0610 in more than 250 patients has found the compound to be generally well tolerated. As of October 17, 2019, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated in each arm of the MANIFEST trial. Prior to initiating the MANIFEST study, we demonstrated that CPI-0610 was generally well tolerated across three Phase 1 clinical trials in which we treated a total of 138 patients with a variety of hematological malignancies. In a Phase 1 trial in lymphoma, we identified the maximum tolerated dose of 225 mg per day. We have seen evidence of clinical activity at a range of doses below this maximum tolerated dose, including the 125 mg starting dose being used in MANIFEST. We can titrate the dose upward to 225 mg per day and have done so without additional toxicity. We believe this potentially favorable therapeutic window may differentiate CPI-0610 from some other BET inhibitors. The dose-limiting toxicity for other BET inhibitors, which is thrombocytopenia, has been shown in CPI-0610 to be dose-dependent, non-cumulative, and reversible at the maximum tolerated dose of 225 mg in MF patients treated to date. See *Our Product Candidates/CPI-0610—BET Inhibitor/Safety* below for more information about the compound's safety profile.

EZH2 Franchise

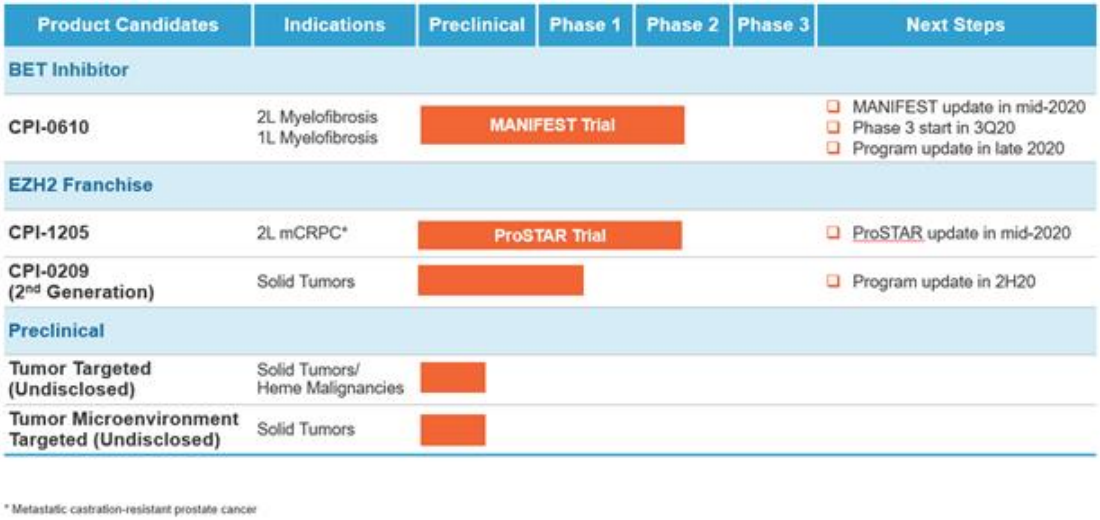
CPI-1205 is a small molecule designed to promote anti-tumor activity by specifically inhibiting EZH2, an enzyme that suppresses target gene expression. Based on insights from our platform and the advancing body of scientific literature supporting the role of EZH2 in certain tumor types, including prostate cancer, we prioritized clinical development of CPI-1205 as a combination therapy for mCRPC. We are currently conducting ProSTAR, an open-label Phase 1b/2 clinical trial of CPI-1205 for the treatment of mCRPC in combination with the ARS inhibitors enzalutamide (marketed as Xtandi®) or abiraterone acetate (marketed as Zytiga®). Abiraterone acetate is dosed with prednisone, which is the current clinical practice.

We believe that preliminary data from ProSTAR suggest that CPI-1205 has the potential to offer meaningful benefits beyond the current standard of care. We have seen preliminary evidence of reductions in prostate-specific antigen, or PSA; reductions in circulating tumor cells, or CTCs; tumor shrinkages; and extended duration of response for some patients in ProSTAR. We disclosed Phase 1b data from ProSTAR at the AACR meeting on April 1, 2019. See the section below titled *Our Product Candidates/CPI-1205—EZH2 Inhibitor/Clinical Development* for more information. We aim to provide an additional update and a decision on further development of the compound in mid-2020. If the ProSTAR trial is successful, a determination that will be based in part on data on durability of effect and on biomarkers to identify target patient populations likely to benefit, we expect to initiate a pivotal Phase 3 clinical trial of CPI-1205 in combination with either enzalutamide or abiraterone acetate for the treatment of mCRPC. A clear signal is required to move the program into Phase 3.

We believe that targeting EZH2 has the potential for broad therapeutic application in a variety of tumor types, and we have taken a franchise approach to targeting EZH2. We believe that CPI-0209, our second-generation and potentially best-in-class EZH2 inhibitor, may enable us to address additional patient populations beyond those that have been targeted by first-generation EZH2 inhibitors such as CPI-1205. Based on this belief, we designed CPI-0209 to achieve comprehensive coverage of EZH2. We have seen evidence of preclinical activity of CPI-0209 both as a single agent and in combination with other agents. We believe this compound has potentially broad application in several solid tumors and hematological malignancies. We initiated a Phase 1 dose-escalation trial with CPI-0209 in September 2019.

Our Pipeline

The following table summarizes key information about our most advanced programs:



* Metastatic castration-resistant prostate cancer

We have retained global development and commercial rights to all of our product candidates. Our goal is to become a fully integrated oncology company, with a broad pipeline of development and discovery programs as well as commercial products in the future. Our management team has extensive experience, including senior roles at leading pharmaceutical companies in the discovery, development, regulatory review, and commercialization of cancer therapeutics.

We have a preclinical pipeline of compounds that target the microenvironment of solid tumors and hematological malignancies, as well as compounds that target innate immunity in solid tumors. We aim to test these molecules in clinical trials in indications with a defined biological rationale, utilizing trial designs that are supported by biomarkers for patient enrichment.

Our Strategy

Our objective is to discover, develop, and commercialize innovative drugs that address the serious unmet medical needs of patients with cancers that are associated with abnormal gene expression or drug resistance. To achieve our objective, we aim to:

- ***Continue to study the safety and efficacy of our clinical-stage compounds.*** Building on the evidence of clinical activity that we have observed to date in our ongoing clinical trials of CPI-0610 and CPI-1205, we aim to advance our EZH2 and BET programs further in 2020.
- ***Initiate a Phase 3 clinical trial of CPI-0610 in MF.*** Having generated preliminary clinical data demonstrating evidence of clinical activity of CPI-0610 across a broad range of parameters in patients with MF, we plan to initiate a Phase 3 clinical trial for CPI-0610 in third quarter of 2020.
- ***Determine next steps for CPI-1205.*** Having generated preliminary data that CPI-1205 provided deep and durable effects in a subset of heterogeneous mCRPC patients, we aim to gather additional clinical data, including data on durability of effect and on biomarkers to identify target patient populations likely to benefit, in order to make a decision about the further development of the compound in mid-2020, including whether to initiate a Phase 3 clinical trial.
- ***Advance clinical testing of CPI-0209.*** We believe CPI-0209 is a potential best-in-class EZH2 inhibitor. In 2020, we aim to gather initial safety data with CPI-0209 monotherapy in patients with solid tumors from our ongoing Phase 1 study. We also aim to determine the recommended Phase 2 dose for CPI-0209 monotherapy in order to begin Phase 2 expansion trials in patients with certain advanced solid tumors and to begin a Phase 1 dose escalation phase of the trial in combination with chemotherapy.
- ***Advance our preclinical portfolio to generate additional assets with compelling clinical development paths.*** We are leveraging our platform to discover and develop programs focused on the inhibition of epigenetic regulators of tumor and/or immune cells that may lead to the killing or reprogramming of cancer cells and/or result in anti-tumor immune activity.

- ***Maximize the global commercial potential of our product candidates.*** We currently plan to retain commercial rights to our product candidates in the United States while selectively evaluating strategic partnerships that could maximize their commercial potential by expanding our geographic reach or by development in additional indications.

Cancer and Epigenetics

Cancer is a heterogeneous group of diseases characterized by uncontrolled cell division and growth. Cancer can arise when the dysregulation of the affected cell's gene expression program alters the identity and function of normal cells. This dysregulation can arise when there are changes in genes that control cell identity. Cancer cells can utilize modulation of gene expression in part by using epigenetic regulators to activate pro-tumor genes or deactivate tumor suppressor genes. Furthermore, cancer cells can also use epigenetic regulators to activate resistance mechanisms against cancer treatments, including chemotherapy, targeted therapy, and immunotherapy, and render the treatments less effective.

Epigenetics refers to a broad regulatory system that controls gene expression by modifying chromatin, which consists of DNA wrapped around an assembly of proteins called histones. The DNA included in chromatin is identical in each cell in the body. The identity and function of each cell is determined by the specific set of genes that are expressed, or turned on or off, in a given cell. Whether a specific set of genes is turned on or off depends on the action of epigenetic regulators.

Our Approach

We are a pioneer in the discovery and development of novel therapeutics that target various classes of epigenetic regulators and modulate gene expression in a more selective manner than early epigenetic drugs. Our efforts have demonstrated that these distinct classes of epigenetic regulators are broadly druggable and that selective reprogramming of gene expression is a promising therapeutic approach not only to induce cancer cell killing but also to enhance anti-tumor immunity.

Integrated Platform

Our integrated epigenetics platform includes a deep understanding of the biological context in which epigenetic regulators operate, the development of small-molecule product candidates that selectively modulate their activity, and the design of clinical development programs supported by novel biomarker strategies.

Our approach to therapeutic agents to date has been focused on epigenetic targets:

- whose inhibition modulates gene expression in a highly selective manner;
- with broad development opportunities, including biomarker-defined contexts, which we believe may expand the applicability of our product candidates to cancers with immune evasion or acquired drug resistance; or
- whose inhibition may reprogram immune-suppressive immune cells in the tumor microenvironment to enhance anti-tumor activity.

Our epigenetics platform allows us to identify potential product candidates that intervene in diseases by targeting distinct classes of epigenetic regulators, including the following examples:

- EZH2—an epigenetic *writer*—is an enzyme that suppresses target gene expression by adding modifications to chromatin. Certain cancer and immune cells can use EZH2 to promote growth of cancer cells or suppress an anti-tumor immune response; and
- BET proteins—a group of epigenetic *readers*—are proteins that bind to chromatin and enhance target gene expression. Certain cancer cells can use BET proteins to promote growth of cancer cells and inflammatory disorders

We are also currently advancing several discovery programs against undisclosed epigenetic regulators focused on the tumor microenvironment and the immune microenvironment.

Our Product Candidates

CPI-0610—BET Inhibitor

Overview

BET proteins are epigenetic readers that turn on specific genes by binding unique regions of the genome through their ability to read specific chemical tags on chromatin. In some instances, BET proteins turn on genes that are abnormally expressed in a variety of human cancers. BET inhibitors downregulate the expression of oncogenes, which are key genes that have the potential to cause cancer, such as MYC or NF-κB target genes, and effectively kill many cancer cell lines in *in vitro* models. These observations resulted in the generation and clinical investigation of BET inhibitors in several cancer subtypes. We have observed preclinical activity in cancer subtypes that are driven by NF-κB signaling.

CPI-0610 is a small molecule designed to promote anti-tumor activity by specifically inhibiting the bromodomain function of BET proteins, which normally enhance target gene expression. Our epigenetics platform reflects our deep understanding of the biological contexts in which BET proteins operate, including cancer pathways that are highly sensitive to CPI-0610. A combination of our preclinical studies, as well as translational insights from our first-in-human study of CPI-0610, led us to prioritize the clinical development of CPI-0610 in MF.

We are currently enrolling patients in MANIFEST, an open-label Phase 2 clinical trial of CPI-0610 as a first-line or second-line treatment for MF, a progressive hematological cancer. We are testing CPI-0610 in combination with ruxolitinib in the first-line setting in ruxolitinib-naïve patients. We are also testing CPI-0610 as a monotherapy and in combination with ruxolitinib treatment in the second-line setting in patients who are refractory to, have an inadequate response to, or are intolerant of ruxolitinib. Preliminary data showed signs of clinical activity across a broad range of parameters, suggesting possible disease-modifying effects of CPI-0610. We believe that evidence of hemoglobin improvement with CPI-0610 may provide a benefit to patients with anemia, which is associated with both myelofibrosis itself and with treatment by ruxolitinib. See the section below titled *Our Product Candidates/CPI-0610—BET Inhibitor/Clinical Development* for more information.

We believe that the compound may have a differentiated safety profile compared with some other BET inhibitors. Clinical testing of CPI-0610 in more than 250 patients has found the compound to be generally well tolerated. As of October 17, 2019, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated in each arm of the MANIFEST trial. Prior to initiating the MANIFEST study, we demonstrated that CPI-0610 was generally well tolerated across three Phase 1 clinical trials in which we treated a total of 138 patients with a variety of hematological malignancies. In a Phase 1 trial in lymphoma, we identified the maximum tolerated dose of 225 mg per day. We have seen evidence of clinical activity at a range of doses below this maximum tolerated dose, including the 125 mg starting dose being used in MANIFEST. We can titrate the dose upward to 225 mg per day and have done so without additional toxicity. We believe this potentially favorable therapeutic window may differentiate CPI-0610 from some other BET inhibitors. The dose-limiting toxicity for other BET inhibitors, which is thrombocytopenia, has been shown in CPI-0610 to be dose-dependent, non-cumulative, and reversible at the maximum tolerated dose of 225 mg in MF patients treated to date. See *Our Product Candidates/CPI-0610—BET Inhibitor/Safety* below for more information about the compound's safety profile.

Based on these preliminary activity and safety data, we are currently planning to advance CPI-0610 into a Phase 3 clinical trial in the third quarter of 2020 after consultation with the FDA and the EMA.

BET Inhibition in Cancer

Abnormal BET function has been implicated in cancer through several means, including chromosomal translocation and gene amplification and overexpression whereby oncogenic and inflammatory signals are turned on in cancer cells through altered BET activity.

Of note, BET proteins control the expression of the target genes of NF-κB, a key immune signaling pathway that is abnormally activated in various diseases, including cancer and immune disorders. NF-κB signaling has been shown to be abnormally high in some hematological malignancies, such as MF and activated B cell-like diffuse large B-cell lymphoma, or ABC-DLBCL. In preclinical studies in MF, animals treated with BET inhibitors alone or in combination with a JAK1/JAK2 inhibitor displayed a reduction in NF-κB target gene expression, improvement in bone marrow fibrosis, and reduced disease burden.

In addition, BET proteins promote the generation of megakaryocytes from hematopoietic stem cells. We believe that the blood cells most responsible for bone marrow scarring in MF are dysfunctional megakaryocytes, which proliferate and produce inflammatory molecules in part through elevated NF-κB signaling.

Myelofibrosis

MF is part of a collection of progressive blood cancers known as myeloproliferative neoplasms and is associated with significantly reduced quality of life and shortened survival. As the disease progresses, the bone marrow produces fewer red blood cells, often leading to severe anemia (a condition characterized by low red-blood-cell counts) and red-blood-cell transfusion requirements. In addition, within one year of diagnosis, the incidence of thrombocytopenia increases significantly. Thrombocytopenia is a condition characterized by low platelet counts in the blood. Among other complications, most patients with MF have enlarged spleens as well as many other physical symptoms, including abdominal discomfort, bone pain, and extreme fatigue.

There are limited treatment options for patients with MF. Currently the JAK inhibitors ruxolitinib and fedratinib are the only approved products for MF, and there are no approved products for patients whose MF progresses after treatment with these products. Ruxolitinib is the current standard of care in intermediate- to high-risk MF. Ruxolitinib inhibits dysregulated janus kinase 1 and 2, or JAK1/JAK2, signaling that is associated with MF. Ruxolitinib produces spleen reduction and symptom improvement in MF patients. However, its side effects include increased anemia and transfusion dependence. In the SIMPLIFY-1 clinical trial of ruxolitinib in JAK1/ JAK2-inhibitor-naïve patients, transfusion dependence increased from 24.0% to 40.1% after 24 weeks of treatment with ruxolitinib. Ruxolitinib has not been shown to significantly reverse bone marrow fibrosis, a condition that has been documented as a primary cause of morbidity and mortality in MF. As a result of these factors, many patients cannot, or choose not to, initiate ruxolitinib therapy. Many other patients may not tolerate treatment with, or will have an insufficient response to, ruxolitinib. Patients generally have poor prospects for survival following discontinuation of therapy with ruxolitinib.

We believe that at least two-thirds of the 17,000 to 20,000 MF patients in the United States are intermediate- or high-risk patients and are therefore eligible for systemic treatment, including ruxolitinib. Incyte Corporation, or Incyte, which markets ruxolitinib, has estimated that about half of these eligible patients receive treatment with ruxolitinib, which is the standard of care. Based on preliminary data from the MANIFEST trial, we aim to demonstrate that virtually all patients eligible for, or taking, ruxolitinib could benefit from taking the combination of CPI-0610 and ruxolitinib. We aim to show that CPI-0610 in combination with ruxolitinib is associated with increased spleen volume reduction and symptom improvement compared to ruxolitinib alone. In addition, some MF patients, such as anemic patients, who might delay taking ruxolitinib due to anemia associated with the disease or with ruxolitinib therapy may benefit from initiating on the CPI-0610/ruxolitinib combination due to preliminary evidence of hemoglobin improvement and conversion to transfusion independence. CPI-0610 monotherapy may also provide benefit for patients who have discontinued treatment with ruxolitinib due to side effects or MF progression.

Clinical Development

Phase 2 Clinical Trial. We are currently conducting MANIFEST, a Phase 2 clinical trial of CPI-0610 as a monotherapy and in combination with ruxolitinib (marketed as Jakafi®/Jakavi®) in patients with myelofibrosis, or MF, a progressive hematological cancer. We are enrolling MF patients who are Janus-kinase-1/2-, or JAK1/JAK2-, inhibitor-naïve, a first-line setting, as well as patients who are refractory to or intolerant of, or have had a sub-optimal response to, ruxolitinib, a second-line setting. In the first-line setting, we are testing CPI-0610 in combination with ruxolitinib in JAK1/JAK2-inhibitor-naïve patients with the aim of measuring spleen volume reduction and symptom improvement, among other relevant parameters. In the second-line setting, we are stratifying patients for dependence on red-blood-cell, or RBC, transfusions. In transfusion-dependent, or TD, patients, we are measuring conversion to transfusion independence, or TI, in addition to spleen volume reduction and symptom improvement. In non-TD patients, we are measuring spleen volume reduction and symptom improvement, among other relevant parameters.

On December 9, 2019, updated preliminary data from MANIFEST were presented at the Annual Meeting of the American Society of Hematology, or ASH. We believe that these preliminary data from MANIFEST suggest that CPI-0610 has the potential to offer meaningful benefits beyond the current standard of care in MF and may have disease-modifying effects. As of October 17, 2019, an aggregate of 120 patients were enrolled in MANIFEST.

One presentation related to Arms 1 and 2 of MANIFEST, in which we are evaluating CPI-0610, either as a monotherapy (Arm 1) or in combination with ruxolitinib (Arm 2) in ruxolitinib-refractory or -intolerant patients with MF. The second presentation related to Arm 3, in which we are evaluating the combination of CPI-0610 and ruxolitinib in JAK1/JAK2-inhibitor-naïve patients with MF.

The presentation relating to Arms 1 and 2 included updated preliminary data as of October 17, 2019 that showed signs of clinical improvement in spleen volume reduction, patient-reported symptom improvement, hemoglobin increases, bone marrow fibrosis score improvement and conversion to transfusion independence in transfusion-dependent patients. As of October 17, 2019, in Arm 2, six of 14 ruxolitinib-refractory or -intolerant patients who were TD at baseline had converted to TI. Neither of the two ruxolitinib-refractory or -intolerant patients in Arm 1 who were TD at baseline had converted to TI as of October 17, 2019.

The presentation relating to Arm 3 included preliminary data as of October 17, 2019, that showed signs of CPI-0610 clinical activity in JAK1/JAK2-inhibitor-naïve patients. As of October 17, 2019, 12 of 15 evaluable JAK1/JAK2-inhibitor-naïve patients treated with a combination of CPI-0610 and ruxolitinib for at least 12 weeks experienced at least a 35% reduction in spleen volume from baseline, or SVR35, and ten of 14 evaluable patients reported at least a 50% reduction in Total Symptom Score, or TSS50, both of which are measures of clinical activity that have been the basis for approval of other existing MF treatments.

As a result of preliminary data in JAK1/JAK2-inhibitor-naïve patients and in TD ruxolitinib-refractory or -intolerant patients, we have expanded enrollment in all three arms. We expanded Arm 3 for JAK1/JAK2-inhibitor-naïve patients from 43 patients to up to 101 patients. We expanded Cohort 1A in Arm 1 and Cohort 2A in Arm 2, which are the cohorts that include TD patients, from 16 to up to 60 patients. We are planning for a potential pivotal trial in the 1L setting that we expect to begin in 2020.

Arm 1: CPI-0610 Monotherapy in Ruxolitinib-Refractory or -Intolerant Patients (2L)

In this arm, patients are treated in a 21-day dosing cycle and are administered CPI-0610 starting at 125 mg once per day, which may be titrated up to 225 mg, with 14 days on treatment and seven days off treatment. The primary endpoints are the proportion of patients who achieve at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment for non-TD patients and the rate at which TD patients convert to TI for patients who were TD at baseline.

The tables below present updated preliminary data as of October 17, 2019 from Arm 1 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	36
Number of patients evaluable for efficacy	15
SVR35, best response	1 of 13 evaluable[1]
SVR35 at 24 weeks	0 of 9 evaluable[2]
SVR	11 of 13 evaluable[1]
SVR (%), median best change	-26.8%
SVR (%), median best change range	-57.5% to 10.8%
TSS50, best response	6 of 10 evaluable[1]
TSS50 at 24 weeks	3 of 6 evaluable[2]
TSS (%), median best change	-58.3%
TSS (%), median best change range	-90.1% to 13.4%
PGIC improvement, number of patients	14 of 15 evaluable[1]
PGIC much / very much improved	10 of 15 evaluable[1]
Hemoglobin increase of at least 1.5 mg/dL	6 of 11
Improvement in bone marrow fibrosis	2 of 9 evaluable[3]
TD to TI conversion	0 of 2 evaluable

TSS = Total Symptom Score, a clinical tool for recording patient-reported outcomes

PGIC = Patient Global Impression of Change, a clinical tool for recording patient-reported outcomes

TD = Transfusion Dependent, defined as receiving an average of ≥ 2 RBC transfusions per month during the 12 weeks prior to enrollment

TI = transfusion independent, defined as absence of RBC transfusions over any consecutive 12-week period

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for ≥ 12 weeks

(2) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for ≥ 24 weeks

(3) quantification of bone marrow cellularity is scored to one of four grade categories based on a review by a pathologist

Arm 2: CPI-0610 Add-On to Ruxolitinib in Ruxolitinib-Refractory or -Intolerant Patients (2L)

In this arm, CPI-0610 is added to treatment with ruxolitinib and CPI-0610 is dosed according to the schedule as in Arm 1 and patients continue treatment with ruxolitinib at their last stable dose with no titration of ruxolitinib. The primary endpoints are the proportion of patients who achieve at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment for non-TD patients and the rate at which TD patients convert to TI for patients who were TD at baseline.

The tables below present updated preliminary data as of October 17, 2019, from Arm 2 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	54
Number of patients evaluable for efficacy	33
SVR35, best response	5 of 32 evaluable[1]
SVR35 at 24 weeks	3 of 25 evaluable[2]
SVR	29 of 32 evaluable[1]
SVR (%), median best change	-17.1%
SVR (%), median best change range	-53.6% to 4.7%
TSS50, best response	19 of 31 evaluable[1]
TSS50 at 24 weeks	12 of 26 evaluable[2]
TSS (%), median best change	-61.8%
TSS (%), median best change range	-100% to 0.9%
PGIC improvement	30 of 33 evaluable[1]
PGIC much / very much improved	23 of 33 evaluable[1]
Hemoglobin increase of at least 1.5 mg/dL	2 of 15
Improvement in bone marrow fibrosis	10 of 23 evaluable[3]
TD to TI conversion	6 of 14 evaluable

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for ≥ 12 weeks

(2) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for ≥ 24 weeks

(3) quantification of bone marrow cellularity is scored to one of four grade categories based on a review by a pathologist

In Cohort 2A, which enrolled patients that were TD at baseline, three of 12 evaluable patients had a SVR35 response at week 24 and the evaluable patients had a median best percent change in spleen volume of -24.9%. Seven of 13 evaluable patients had a TSS50 response at week 24 and the evaluable patients had a median best percent change in TSS of -58.8% and nine of 12 evaluable patients reported PGIC improvement at 24 weeks. For the patients in this cohort evaluable after 12 weeks, five of 17 evaluable patients had a SVR35 response at any time (best response) and the evaluable patients had a median best percent change in spleen volume of -21.2%. Thirteen of 17 evaluable patients had a TSS50 response at any time (best response) and the evaluable patients had a median best percent change in TSS of -71% and 16 of 18 evaluable patients reported PGIC improvement.

In Cohort 2B, which enrolled patients that were not TD at baseline, no evaluable patients (0 of 13) had a SVR35 response at week 24 and the evaluable patients had median best percent change in spleen volume of -10.9%. Five of 13 evaluable patients had a TSS50 response at week 24, and the evaluable patients had a median best percent change in TSS of -44.1% and nine of 13 evaluable patients reported PGIC improvement at 24 weeks. For the patients in this cohort evaluable after 12 weeks, no patients (0 of 15) had a SVR35 response at any time (best response) and the evaluable patients had a median best percent change in spleen volume of -15.8%. Six of 14 evaluable patients had a TSS50 response at any time (best response) and the evaluable patients had a median best percent change of -49% and 14 of 15 evaluable patients reported PGIC improvement.

Arm 3: Combination of CPI-0610 and Ruxolitinib in JAK1/JAK2-Inhibitor-Naïve Patients (1L)

In this arm, patients are treated with CPI-0610 according to the schedule as in Arm 1 and receive either 10 mg or 15 mg twice per day of ruxolitinib, depending on the platelet count at baseline, with the ability to titrate up to a maximum dose of 20 mg twice per day. The primary endpoints are the proportion of patients who achieve at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment.

The tables below present updated preliminary data as of October 17, 2019, from Arm 3 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	30
Number of patients evaluable for efficacy	15 (SVR35) / 14 (TSS50)
SVR35, at 12 weeks	12 of 15 evaluable[1]
SVR (%), median change at 12 weeks	-49.7%
SVR (%), median change range at 12 weeks	-80.8% to -17.0%
TSS50, 12 weeks	10 of 14 evaluable[1]
TSS (%), median change at 12 weeks	-60.3%
TSS (5), median change range at 12 weeks	-100% to 90.2%

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for ≥ 12 weeks

Safety

As of October 17, 2019, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated in each arm of the MANIFEST trial. In Arm 1, 34 patients remained active on treatment and two had discontinued. In Arm 2, 41 patients remained on active treatment and 13 had discontinued, including one patient who was initially transplant ineligible, who underwent stem cell transplantation after six cycles of CPI-0610 add-on to ruxolitinib treatment. All 30 patients in Arm 3 remained active on treatment as of October 17, 2019.

Three patients in Arm 2 discontinued treatment due to grade 5 (fatal) adverse events. These adverse events consisted of acute kidney injury, traumatic subdural hematoma (patient tripped and fell) and brain stem hemorrhage (patient without concomitant thrombocytopenia). We assessed the acute kidney injury as unlikely related to CPI-0610 and unlikely related to ruxolitinib. The clinical investigator assessed the acute kidney injury as possibly related to CPI-0610 and not related to ruxolitinib. We believe the acute kidney injury event was likely related to the concomitant use of other medications and possibly due to progression of disease. We and the relevant clinical investigator assessed the two other deaths as unrelated to CPI-0610.

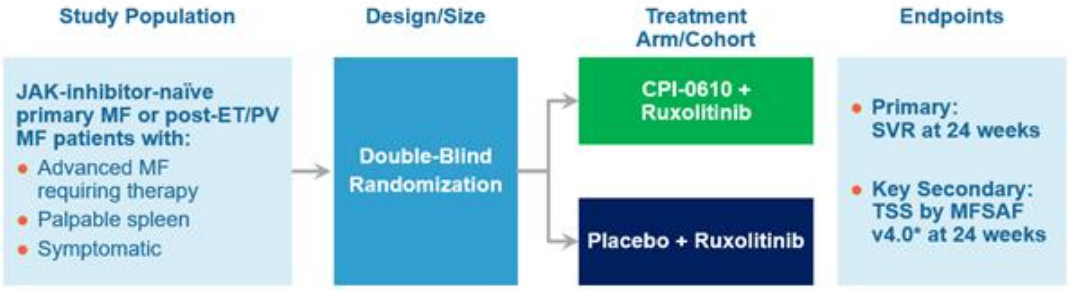
The most common treatment-emergent adverse events, or TEAEs, of any grade observed in Arm 1 included diarrhea, nausea, headache, cough, vomiting, thrombocytopenia, dysgeusia, back pain, upper respiratory tract infection and hyperuricemia, each of which occurred in 10% or more of patients. The most frequently observed grade 3 or higher TEAEs irrespective of causality in Arm 1 were dyspnea (three patients), anemia (two patients), diarrhea (two patients), thrombocytopenia (two patients), hyponatremia (two patients), and neutropenia (two patients). TEAEs of grade 3 or higher considered related to CPI-0610 consisted of diarrhea and thrombocytopenia (two patients each), constipation, decreased appetite, diarrhea, dyspnea, neutropenia, rash, taste disorder, and upper abdominal pain (one patient each).

The most common TEAEs of any grade observed in Arm 2 included diarrhea, thrombocytopenia (including platelet count decrease), nausea, fatigue, cough, upper respiratory tract infection, vomiting, constipation, pain in extremity, peripheral edema, contusion, abdominal distension, decreased appetite, paresthesia, and arthralgia, each of which occurred in 10% or more of patients. The most frequently observed grade 3 or higher TEAEs irrespective of causality in Arm 2 were thrombocytopenia (including platelet count decrease) (seven patients), anemia (four patients), fatigue (three patients) and pneumonia (three patients). TEAEs of grade 3 or higher considered related to CPI-0610 by clinical investigator consisted of thrombocytopenia (including platelet count decrease) (seven patients), anemia (three patients), diarrhea and fatigue (two patients each), acute kidney injury, blood creatinine increase, nausea, neutropenia, and vomiting (one patient each).

The most common TEAEs of any grade observed in Arm 3 included diarrhea, anemia, nausea, thrombocytopenia (including platelet count decrease), dizziness, muscle spasms, constipation, dyspnea, and mouth ulceration, each of which occurred in 10% or more of patients. There were three patients with grade 3 anemia and one patient with grade 4 thrombocytopenia who required a dose interruption for three weeks.

MANIFEST Expansion and Future Updates

As a result of preliminary data in JAK1/JAK2-inhibitor-naïve patients and in TD ruxolitinib-refractory or -intolerant patients, we have expanded the treatment arms for these patients in MANIFEST. We expanded Arm 3 for JAK1/JAK2-inhibitor-naïve patients from 43 to up to 101 patients. We also expanded Cohort 1A (TD ruxolitinib-refractory, -resistant, or -ineligible patients being treated with being treated with CPI-0610 monotherapy) and Cohort 2A (TD patients adding CPI-0610 to existing ruxolitinib treatment due to suboptimal response or MF progression) from 16 to up to approximately 60 patients. We aim to provide 24-week data from approximately 25-30 evaluable JAK1/JAK2-inhibitor-naïve MF patients as well as 70-80 second line patients from MANIFEST at a medical meeting in mid-2020 and further updates in the second half of 2020. We expect to begin a Phase 3 trial with CPI-0610 + ruxolitinib versus placebo + ruxolitinib in ruxolitinib-naïve MF patients in the second half of 2020 after consultation with the FDA and the EMA. Below is the planned design of the Phase 3 trial:



CPI-1205—EZH2 Inhibitor

Overview

Historically, the primary focus of EZH2 as a drug target has been the role of EZH2 mutations or overexpression in cancer. We believe these genetically defined approaches to EZH2 inhibition may underestimate the broader therapeutic potential of the target in cancer. EZH2 genomic aberrations and overexpression are frequently correlated with late-stage cancer and a poor prognosis for a wide variety of cancers, including prostate cancer. Furthermore, EZH2 also cooperates with other cancer-promoting pathways, such as androgen receptor signaling and immune signaling. Therefore, we believe EZH2 inhibition can synergistically enhance the effectiveness of existing cancer therapies.

EZH2 Inhibition in Cancer

EZH2 acts as an epigenetic writer and normally regulates gene expression by placing one or more methyl groups on a histone protein leading to the suppression of gene expression programs. While this effect of EZH2 on gene expression is a normal part of cellular development, some cancers depend on an abnormal pattern of gene expression and re-direct EZH2 to genes that become abnormally repressed. Cancer cells with these abnormal gene expression programs may be more resistant to anti-cancer therapies.

Abnormal EZH2 function has been implicated in cancer in a number of ways:

- Cancer genetics: mutations in the gene encoding EZH2 result in the altered enzymatic activity of EZH2, and cancer cells become dependent on this abnormal activity for tumor growth. Alternatively, mutations in other epigenetic regulators can change the genes expressed by cancer cells and indirectly create a dependence on EZH2 for cancer cell growth;
- Acquired drug resistance: therapeutic agents promote EZH2-mediated gene silencing that may lead to acquired resistance to these agents; and
- Immune suppression: EZH2 mediates reprogramming of immune cells within the tumor, e.g., T-cells, and tumor cells to create an immune-suppressive tumor microenvironment.

Metastatic Castration-Resistant Prostate Cancer

According to the American Cancer Society, or ACS, prostate cancer is the second most common type of cancer among men in the United States and the second leading cause of cancer death in this population. The ACS estimates that in the United States more than 190,000 men will be diagnosed with prostate cancer and more than 33,000 men will die from prostate cancer in 2020.

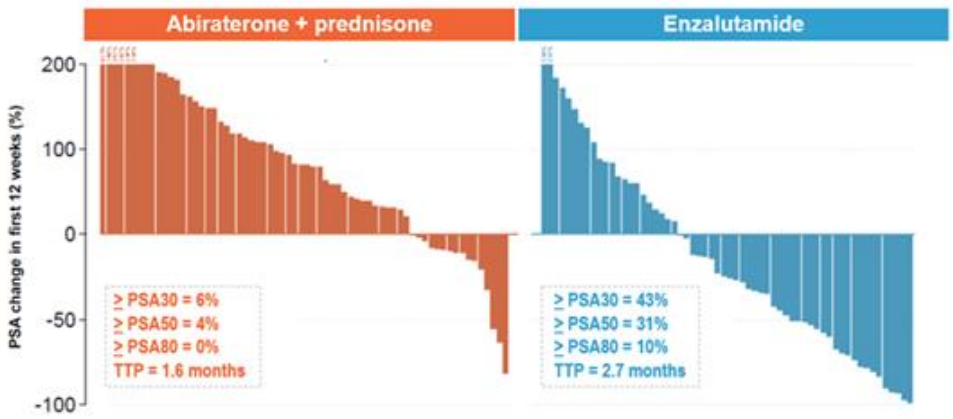
The growth and survival of prostate cancer cells depend primarily on the androgen receptor signaling pathway. Cancer cells can use the binding of androgens to androgen receptors to trigger abnormal cell growth and tumor progression. The standard of care for the treatment of advanced prostate cancer is androgen deprivation therapy, or ADT, which induces medical castration or surgical castration to achieve reduced testosterone levels. Medical castration involves gonadotropin-releasing hormone antagonists, alone or in combination with first-generation anti-androgen therapy. Most men with prostate cancer treated with ADT respond, as measured by tumor regression, relief of symptoms, and reductions in serum PSA levels and are considered to have hormone-sensitive prostate cancer. However, almost all prostate cancer patients eventually experience a recurrence in tumor growth despite ADT. These patients are diagnosed with castration-resistant prostate cancer, or CRPC, which refers to prostate cancer that progresses despite ADT and is characterized by low serum testosterone levels. The development of CRPC following ADT is due in part to tumor cells that adapt to the hormone-deprived environment of the prostate.

Castration-resistant prostate cancer that spreads, or metastasizes, to other parts of the body is diagnosed as mCRPC and may be characterized by increasing PSA levels, elevated circulating tumor cells (CTC) counts, bone metastases, and soft tissue disease. CTCs are cells that have been shed from a primary tumor and are carried around the body in the blood and may lead to metastases.

Patients with mCRPC have an average survival of approximately 30 months and experience a deterioration in quality of life despite treatment with the available therapeutic options. The standard practice is to treat mCRPC with an ARS inhibitor, including abiraterone acetate or enzalutamide. These products are approved in the United States for first-line therapy in chemotherapy-naïve patients with mCRPC as well as for second-line treatment in patients who have received prior chemotherapy.

We believe that there are approximately 140,000 men in the United States living with castration-resistant prostate cancer and that the majority of those patients will develop mCRPC. Based on third-party data, we estimate that there are approximately 30,000 to 50,000 new mCRPC patients per year in the United States. Most patients progress from earlier prostate cancer stages, while some patients are initially diagnosed with metastatic disease. We believe that most patients with mCRPC receive treatment with at least one ARS inhibitor. According to published literature, approximately 60-80% of patients with mCRPC respond to first-line treatment with either abiraterone acetate or enzalutamide, with nine to 15 months of PSA progression-free survival. Of those who have a PSA response, a large majority eventually develop resistance to ARS inhibitors. Resistance mechanisms to ARS inhibitors include AR amplification and overexpression and circulating androgen receptor splice variant-7, or ARV7, which is a constitutively active version of the AR that is no longer inhibited by ARS inhibitors. ARV7 is a marker for aggressive mCRPC. When patients' response to this first-line therapy becomes inadequate, second-line therapy generally consists of switching patients to the other approved ARS inhibitor. Data from a study presented at the 2018 meeting of the American Society of Clinical Oncology by Dr. Kim Chi of the Vancouver Prostate Centre showed the following PSA responses and time to progression for abiraterone acetate use as a second-line treatment after enzalutamide and enzalutamide use as a second-line treatment after abiraterone acetate:

Prostate-Specific Antigen (PSA) Responses and Time to Clinical Progression (TTP) With Second-Line Abiraterone + Prednisone and Second-Line Enzalutamide Therapy Found in Kim Chi Study



CPI-1205 is a small molecule designed to promote anti-tumor activity by specifically inhibiting EZH2. In *in vitro* and *in vivo* models, we observed a dose-proportional inhibition of EZH2 by CPI-1205 that correlated with the tumor-growth-inhibiting activity. We completed a Phase 1 clinical trial of CPI-1205 as a monotherapy in 32 patients with relapsed B-cell lymphoma in which CPI-1205 demonstrated clinical activity and was well tolerated.

We also observed in preclinical studies that CPI-1205 inhibited tumor growth as a single agent and synergistically enhanced the efficacy of cancer therapies, including ARS inhibitors, in a prostate cancer model. Based on these observations and the limited options for patients who progress on ARS inhibitors, we prioritized clinical development of CPI-1205 as a combination therapy with ARS inhibitors in mCRPC.

CPI-1205 Clinical Development

ProSTAR is an open-label Phase 1b/2 clinical trial of CPI-1205, a potent and highly selective small-molecule EZH2 inhibitor, in patients with metastatic castration-resistant prostate cancer (mCRPC) in the second-line setting. The ProSTAR study is evaluating CPI-1205 in combination with either enzalutamide or abiraterone / prednisone ("abiraterone"), which are ARS inhibitors, in mCRPC patients who experienced disease progression while receiving the other ARS inhibitor.

We presented data from the Phase 1b portion of ProSTAR at the American Association for Cancer Research meeting in April 2019. The Phase 1b portion of ProSTAR enrolled 36 patients: 20 in the CPI-1205 + abiraterone arm and 16 in the CPI-1205 + enzalutamide arm. Each arm studied two different dose regimens of CPI-1205 as part of the combination: 800 mg three times daily or 400 mg twice daily + cobicistat. We evaluated cobicistat, which blocks CYP3A4, as a co-medication to increase exposure of CPI-1205.

The Phase 1b portion of this trial was designed to establish the safety, pharmacokinetics, pharmacodynamics, maximum tolerated dose, and recommended Phase 2 dose of CPI-1205 with these agents. As of February 6, 2019, we observed evidence of clinical activity in both arms and in each of the parameters measured—prostate-specific antigen, or PSA, reductions, circulating tumor cell reductions, and objective responses by response evaluation criteria in solid tumors, or RECIST. Clinical activity was observed in both the enzalutamide and abiraterone arms, including best PSA reductions of 50% or more and an objective response by RECIST 1.1 criteria.

All best PSA responses seen in the trial as of February 6, 2019, were 80% or more, which is greater than the pre-defined secondary endpoint of the trial, which is a 50% reduction. All PSA responses were found in AR-V7-negative patients. Two out of 18 total patients, and two out of 10 AR-V7-negative patients, in the abiraterone arm achieved a best PSA reduction of more than 80%. Three out of 16 total patients, and three out of 11 AR-V7-negative patients, in the enzalutamide arm achieved a best PSA reduction of more than 80%. Historically, patients being treated with abiraterone after enzalutamide or with enzalutamide after abiraterone have been shown to achieve poor PSA responses and rapid time to disease progression. Several patients in ProSTAR achieved disease control that exceeded or was approaching six months at the data cutoff while continuing therapy. Duration of effect is important in this context, as radiographic progression-free survival, or rPFS, is likely to be the primary endpoint to be used in any potential Phase 3 clinical trial of CPI-1205 in mCRPC.

CPI-1205 was generally well tolerated in combination with enzalutamide or abiraterone in the Phase 1b portion. The most common treatment-related adverse events were fatigue, diarrhea, and nausea, which were observed in more than 20% of the patients and were usually mild to moderate in severity and manageable with supportive care. In combination with enzalutamide, treatment-related adverse events Grade 3 or higher included fatigue, nausea, and increased ALT, a liver enzyme (n=1; 6.3%, respectively). In combination with abiraterone, treatment-related adverse events Grade 3 or higher included fatigue and increased ALT (n=1; 5%, respectively).

In the Phase 2 portion of ProSTAR, we are enrolling patients in three different contexts: (1) CPI-1205 + enzalutamide in heavily pre-treated patients who have progressed after treatment with each of enzalutamide, abiraterone, and chemotherapy, (2) CPI-1205 + enzalutamide in second-line mCRPC randomized against enzalutamide alone, and (3) CPI-1205 + abiraterone in second-line mCRPC. Enrollment of patients in Phase 2 portion of ProSTAR continues according to plan and is nearly complete. We are working to identify biomarkers that might suggest which patient populations are most likely to achieve deep responses to CPI-1205.

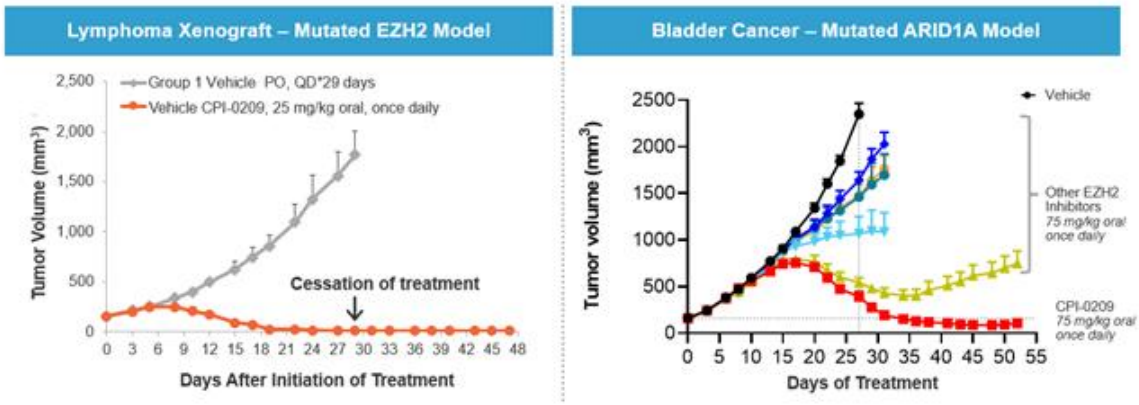
We are shifting the focus of ProSTAR to durability of clinical activity with CPI-1205. An endpoint previously accepted by regulatory authorities for pivotal clinical trials in prostate cancer is radiographic progression-free survival, or rPFS. In addition, we learned from a study presented by the Kim Chi lab at the 2018 ASCO that median responses to second-line therapy generally last only a few months. We are gathering data on time to progression, or TTP, of CPI-1205 in ProSTAR, a metric that may serve as a surrogate of rPFS in guiding future development of the compound. Determining TTP will require additional time for the data set to mature, and we expect to report these data from ProSTAR in mid-2020. Our plans for any potential Phase 3 program for CPI-1205 will depend on our assessment of these data on duration of effect, as well as other considerations.

CPI-0209—Second-Generation EZH2 Inhibitor

We designed CPI-0209, our second-generation EZH2 inhibitor, to achieve comprehensive coverage of EZH2 to potentially enable rapid and durable tumor regression. We believe that such a product could enable us to expand the addressable patient populations beyond those that have been targeted by first-generation EZH2 inhibitors. We are currently conducting the Phase 1 dose escalation portion of a Phase 1/2 clinical trial of CPI-0209 in solid tumors. The Phase 1 dose escalation phase of the clinical trial will study CPI-0209 monotherapy in advanced, relapsed solid tumor patients. After determining the recommended Phase 2 dose for the monotherapy, which we expect to accomplish in 2020, we intend to pursue monotherapy expansion arms in selected solid tumor indications as well as combination therapy development, employing a biomarker strategy that includes assessment of ARID1A and other mutations.

In preclinical studies, we observed that CPI-0209 bound to EZH2 more durably and with higher affinity when compared to first-generation EZH2 inhibitors. We believe that these characteristics may enable CPI-0209 to increase the level and duration of EZH2 inhibition compared to that of first-generation EZH2 inhibitors. Product candidates that provide more comprehensive and longer inhibition of EZH2 may treat certain cancer types requiring that effect. We believe that the level of EZH2 inhibition necessary to produce a therapeutic effect varies across cancer types based on our preclinical studies where we have observed that the dose required to affect tumor growth is higher in certain cancer types. As illustrated below left, we have also observed that CPI-0209 produced tumor regression beginning after five days of initiation of treatment in a lymphoma xenograft mouse model. At right, CPI-0209 demonstrated greater tumor regression in a mutated ARID1A model in bladder cancer compared to other EZH2 inhibitors. Based on this, we hypothesize that CPI-0209 can potentially be effective in other tumor models where first-generation EZH2 inhibitors would be less effective.

Rapid and Durable Tumor Regression in Lymphoma Xenograft Mutated EZH2 Model (left) and Bladder Cancer Mutated ARID1A Model (right)



We plan to develop CPI-0209 for the treatment of solid tumors. We believe that mutations can render these tumor cells dependent on the activity of EZH2 and that cancer cells can use EZH2 as a resistance mechanism against therapeutic agents. We are considering developing CPI-0209 in one or more of these contexts.

Discovery Programs

We are currently advancing several programs against additional epigenetic regulators focused on the tumor and the immune microenvironment. To date, our epigenetics efforts in cancer have been focused on pathways relevant for immune cell re-programming to drive tumor rejection or to increase direct tumor cell killing. We remain committed to advancing programs that normalize abnormal cell gene expression within cancer cells.

Sales and Marketing

In light of our stage of development, we have not yet established a commercial organization or distribution capabilities. We have retained worldwide commercial rights for our product candidates. If our product candidates receive marketing approval, we plan to commercialize them in the United States with our own focused specialty sales force.

Manufacturing

We do not have any manufacturing facilities or personnel. We currently rely on, and expect to continue to rely on, third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. We have entered into clinical supply agreements with contract manufacturers.

We obtain clinical trial materials for CPI-1205, CPI-0610, and CPI-0209 using multiple third-party contract manufacturing organizations. We engage separate third-party manufacturers for producing active pharmaceutical ingredients and other manufacturers for making solid oral drug products

All of our product candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does not require unusual equipment. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience, and scientific resources provide us with competitive advantages, we face competition from many sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a large number of companies developing or marketing treatments for cancer, including many large pharmaceutical and biotechnology companies. In addition, many companies are developing cancer therapies that work by targeting epigenetic mechanisms, including through EZH2 and BET inhibition.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, clinical testing, regulatory review, and marketing than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industry may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites, and enrolling patients in clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our therapeutic product candidates, if approved, are likely to be their efficacy, safety, convenience, and price, the availability and effectiveness of related companion diagnostics in guiding the use of related therapeutics, the level of generic competition, and the availability of reimbursement from government and other third-party payers.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer or more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we can for ours, which could result in our competitors establishing a strong market position before we can enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. Generic products that broadly address these indications are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

The most common methods of treating patients with cancer are surgery, radiation, and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies our product candidates will not compete with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients, and third-party payers.

In addition to currently marketed therapies, there are also a number of products in late-stage clinical development to treat cancer. These products in development may provide efficacy, safety, convenience, and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

If our lead product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below.

CPI-0610 / Myelofibrosis

Ruxolitinib, a JAK1/JAK2 inhibitor developed and marketed by Incyte, was approved by the FDA in 2011 as a first-line treatment for intermediate- and high-risk myelofibrosis patients. Fedratinib (Inrebic®), a JAK2/FLT3 selective inhibitor was approved by the FDA in August 2019 and is now marketed by Bristol-Myers Squibb. There are no products approved by the FDA or regulatory authorities outside the United States as a second-line treatment for patients who no longer respond to or tolerate treatment with ruxolitinib. Many companies are developing product candidates or combination regimens that may compete with CPI-0610, if approved.

Incyte is developing treatments for second-line therapy in patients with MF that combine ruxolitinib with PI3 kinase inhibitors, provirus integration site for moloney murine leukemia virus (PIM) kinase inhibitors, and BET inhibitors. Incyte may develop these combinations in a co-formulated oral dosage form, which could increase the convenience of these combination regimens.

There are several other companies developing JAK1/JAK2 inhibitors as a first-line and second-line treatment of patients with MF. Celgene Corporation, or Celgene, acquired fedratinib in January 2018 as part of its acquisition of Impact Biosciences, Inc. In November 2019, Bristol-Myers Squibb acquired Celgene. Fedratinib has been evaluated in clinical trials as first- and second-line treatments for MF. Celgene has disclosed the intention to combine fedratinib with other products, such as the erythroid maturation agent luspatercept. CTI Biopharma Corp. is conducting a Phase 3 trial of pacritinib in MF patients with severe thrombocytopenia in the United States. On February 10, 2020, CTI disclosed that it had reached agreement with the FDA on an accelerated approval pathway for pacritinib, subject to submission of SVR data from the first 168 patients enrolled in the ongoing Phase 3 PACIFICA trial. Nippon Shinyaku is conducting a Phase 2 trial with NS-018 in patients with MF. Sierra Oncology is developing momelotinib, a JAK1/ACVR1 inhibitor for MF and associated anemia.

CPI-0610 could face competition from products with different biological targets that are in development as a therapeutic option for patients with MF with prior exposure to ruxolitinib, including as a monotherapy or in combination with ruxolitinib. These products include kinase inhibitors, telomerase inhibitors, Bcl-2 inhibitors, and other epigenetic inhibitors. Geron Corporation is conducting a Phase 2 trial evaluating imetelstat, a telomerase inhibitor, in patients with MF who have relapsed after or are refractory to prior treatment with a JAK1/JAK2 inhibitor. Imago BioSciences, Inc., is conducting a Phase 1 trial of IMG-7289 with an inhibitor of LSD1, which is an epigenetic target, in patients with MF. MEI Pharma, Inc., and Helsinn are conducting a Phase 2 trial of pracinostat, a histone deacetylase inhibitor in MF patients on treatment with ruxolitinib. AbbVie is conducting a Phase 2 trial of navitoclax, a Bcl-2 inhibitor in MF patients on treatment with ruxolitinib, and confirmed in February 2020 its intention to launch an additional Phase 3 trial combining navitoclax with ruxolitinib in JAK1/JAK2-inhibitor-naïve patients.

We are aware of several companies that are developing BET inhibitors, including AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Incyte, Boehringer Ingelheim, SignalRx, and Zenith Epigenetics.

CPI-1205 / mCRPC

CPI-1205 could face competition from ARS inhibitors, chemotherapies, and products with alternative mechanisms. Competing ARS inhibitors include enzalutamide (Xtandi®), which is marketed by Pfizer and Astellas, and abiraterone acetate (Zytiga®), which is marketed by Janssen. In late 2018, generic versions of abiraterone acetate were launched.

In addition to direct competition for metastatic castration-resistant prostate cancer patients, earlier use of ARS inhibitors may reduce the number of mCRPC patients suitable for therapy with CPI-1205-containing regimens. Janssen received regulatory approval for abiraterone acetate in combination with androgen deprivation therapy in hormone-naïve metastatic prostate cancer in February 2018. In February 2018, the FDA approved apalutamide (Erleada®), an ARS inhibitor developed by Janssen for the treatment of non-metastatic CRPC, a disease state when the cancer no longer responds to medical or surgical treatments that lower testosterone but has not yet been discovered in other parts of the body. Bayer received FDA approval in July 2019 for darolutamide (Nubeqa®), an ARS inhibitor, plus androgen deprivation therapy (ADT) in non-metastatic CRPC. Bayer is also conducting a Phase 3 clinical trial in metastatic hormone-sensitive prostate cancer. Pfizer and Astellas received FDA approval in December 2019 for enzalutamide in non-metastatic castration-resistant prostate cancer. Each of these products is a potential alternative for CPI-1205-based combination therapy for patients whose disease has progressed after initial treatment with an ARS inhibitor.

Competing chemotherapies include docetaxel (Taxotere), cabazitaxel (Jevtana), and sipuleucel-T (Provenge), which each provide an option for patients who may not wish to continue treatment with an ARS inhibitor. Product candidates targeting prostate-specific membrane antigen (PSMA) include the radioligand Lu-177-PSMA-617 (developed by Endocyte, which was acquired in 2019 by Novartis), AMG160 (Amgen), and HPN424 (Harpoon).

CPI-1205 may also face competition from products with alternative mechanisms of action, including poly-ADP-ribose polymerase, or PARP, inhibitors, targeted therapies including kinase inhibitors, immune checkpoint inhibitors and other immunotherapy-based mechanisms. Several companies are conducting clinical development of PARP inhibitors in prostate cancer, including AstraZeneca/Merck, Clovis Oncology, Pfizer, AbbVie, and Janssen/Glaxo SmithKline. In February 2020, Exelixis announced positive results from a Phase 2 clinical trial with cabozantinib (CABOMETYX®), a kinase inhibitor, combined with atezolizumab (TECENTRIQ®), a checkpoint inhibitor.

CPI-1205 could also face competition from products targeting similar or alternative epigenetic mechanisms. Zenith Epigenetics and GlaxoSmithKline are each testing BET inhibitors (ZEN-3694 and GSK 525762, respectively) in Phase 1 trials in patients with mCRPC. Pfizer initiated clinical development of an EZH2 inhibitor, PF-06821497, in a Phase 1b/2 trial that includes a combination arm with enzalutamide in mCRPC. Jiangsu HengRui is conducting a Phase 1/2 clinical trial of SHR2554, an EZH2 inhibitor, alone or in combination with SHR3680, an androgen receptor antagonist, in mCRPC. CellCentric. is developing CCS1477, a P300/CBP inhibitor, and is conducting Phase 1 clinical trials in prostate cancer. Epizyme, Inc., is conducting Phase 2 clinical trials of tazemetostat, an EZH2 inhibitor, in solid tumors and hematological malignancies and has announced plans to develop the compound in prostate cancer. Tazemetostat (Tazverik®) was approved by the FDA in January 2020 for treatment of patients with epithelioid sarcoma. Merck is conducting Phase 3 clinical trials of pembrolizumab in combination with chemotherapy, enzalutamide, and olaparib in prostate cancer.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business, including by seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of epigenetic small molecule drug discovery.

Our future commercial success depends, in part, 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, misappropriating or violating the valid and enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both our owned and licensed intellectual property, we cannot be sure that patents will issue with respect to any of our owned or licensed pending patent applications or with respect to any patent applications that we or our licensors may file in the future, nor can we be sure that any of our owned or licensed patents or any patents that may be issued in the future to us or our licensors will be commercially useful in protecting our product candidates and methods of manufacturing the same. Moreover, other than for CPI-1205 and CPI-0610, we have generally not sought, and may be unable to obtain, patent protection for certain of our product candidates generally as well as with respect to certain indications. See “Risk factors—Risks related to our intellectual property” for a more comprehensive description of risks related to our intellectual property. We generally file patent applications directed to our key programs, including CPI-1205, CPI-0209 and CPI-0610, in an effort to establish our intellectual property positions regarding new compositions relating to these programs as well as uses of these and similar compositions in the treatment of relevant diseases. We also seek patent protection with respect to methods of making these compositions and to biomarkers that may be useful in establishing or monitoring the efficacy of these compositions in patients. As of January 1, 2020, we owned 24 issued or allowed U.S. patents, 10 U.S. pending non-provisional patent applications, 188 issued or allowed foreign patents, 44 foreign pending patent applications, 12 pending Patent Cooperation Treaty, or PCT, application and 7 U.S. provisional patent applications. The foreign issued patents and patent applications are in a number of jurisdictions, including Australia, Brazil, Canada, Chile, Colombia, Eurasia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Malaysia, Mexico, New Zealand, Philippines, Singapore, and South Africa for CPI-1205 and including Australia, Brazil, Canada, Eurasia, Europe, Hong Kong, India, Israel, Japan, Korea, Mexico, New Zealand, Singapore, and South Africa for CPI-0610 and including Argentina and Taiwan for CPI-0209. Additionally, our epigenetics platform is not protected by any patented intellectual property.

The intellectual property portfolios for our most advanced programs as of January 1, 2020, are summarized below. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the USPTO can be significantly narrowed by the time they issue, if they issue at all. We expect this could be the case with respect to some of our pending patent applications referred to below.

CPI-0610 / BET Inhibitor Program

The intellectual property portfolio for our CPI-0610 program includes patents and applications directed to compositions of matter generically and specifically covering CPI-0610 and related BET inhibitors, as well as to methods for using and making these novel compositions. As of January 1, 2020, we owned three issued or allowed U.S. patents, two issued or allowed European Patent Office patents, five pending PCT applications, and approximately 57 foreign patents and patent applications in a number of other jurisdictions relating to our CPI-0610 program. The U.S. or ex-U.S. issued patents or patents issuing from these pending applications, if any, for our CPI-0610 program are projected to have a statutory expiration date from December 2031 to June 2040, excluding any additional term for patent term adjustments or patent term extensions.

In addition to patent protection, we rely upon unpatented trade secrets and confidential know-how and continuing technological innovation to develop and maintain our competitive position. However, trade secrets and confidential know-how are difficult to protect. We seek to protect our proprietary information, in part, using confidentiality agreements with any future collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. These agreements may not provide meaningful protection. These agreements may also be breached, and we may not have an adequate remedy for any such breach. In addition, our trade secrets and/or confidential know-how may become known or be independently developed by a third party or misused by any collaborator to whom we disclose such information. Despite any measures taken to protect our intellectual property, unauthorized parties may attempt to copy aspects of our products or to obtain or use information that we regard as proprietary. Although we take steps to protect our proprietary information, third parties may independently develop the same or similar proprietary information or may otherwise gain access to our proprietary information. As a result, we may be unable to meaningfully protect our trade secrets and proprietary information. See “Risk factors—Risks related to our intellectual property” for a more comprehensive description of risks related to our intellectual property.

CPI-1205 / EZH2 Inhibitor Program

The intellectual property portfolio for our CPI-1205 program includes patents and applications directed to compositions of matter generically and specifically covering CPI-1205 and related EZH2 inhibitors, as well as to methods for using and making these novel compositions. As of January 1, 2020, we owned seven issued or allowed U.S. patents (including one reissue patent), two issued or allowed European Patent Office patents, five U.S. pending non-provisional patent applications, approximately 82 foreign patents and patent applications in a number of other jurisdictions, and two pending PCT applications relating to our CPI-1205 program. Of our owned U.S. patents, three are issued U.S. composition of matter patents that contain claims covering CPI-1205 specifically and generically. We are aware of prior art that may invalidate some but not all of the generic claims included in one of the composition of matter patents. While we believe that the specific claims and the other generic claims contained in our issued U.S. composition of matter patents provide protection for the composition of matter of CPI-1205 and are not implicated by such prior art, third parties may nevertheless challenge such claims and if such specific claims, or any such other generic claims on which we may rely, are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired. The U.S.- or ex-U.S.-issued patents or patents issuing from these pending applications, if any, for our CPI-1205 program are projected to have statutory expiration dates between February 2033 and December 2039, excluding any additional term for patent term adjustments or patent term extensions.

CPI-0209 / Second-Generation EZH2 Inhibitor Program

The intellectual property portfolio for our CPI-1205 program includes patents and applications directed to compositions of matter generically and specifically covering CPI-1205 and related EZH2 inhibitors, as well as to methods for using and making these novel compositions. As of January 1, 2020, we owned one pending U.S. non-provisional application, three pending PCT applications, one pending U.S. provisional application, and two direct non-PCT filings in Argentina and Taiwan. The U.S. or ex-U.S. issued patents or patents issuing from these pending applications, if any, for our CPI-0610 program are projected to have a statutory expiration date from April 2039 to July 2040, excluding any additional term for patent term adjustments or patent term extensions. While we intend to timely file non-provisional patent applications relating to our provisional patent application, we cannot predict whether any of our future patent applications for CPI-0209 or any other future product candidates will result in the issuance of patents that effectively protect CPI-0209 and any other future product candidates, or if any of our or our licensors’ issued patents will effectively prevent others from commercializing competitive products. 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 and our licensors cannot be certain that we were the first to make the inventions claimed in our licensed patents, patents we own in the future, or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

License and Collaboration Agreements

Research, Development and Commercialization Agreement with the Leukemia & Lymphoma Society

In July 2012, we entered into a research, development and commercialization agreement with the Leukemia & Lymphoma Society, or LLS. We refer to the agreement as the LLS Agreement. Under the LLS Agreement, LLS agreed to provide funding for the development of a compound targeted toward certain tandem bromodomain-containing proteins, designed for and researched for use in the treatment of lymphoma, myelodysplastic syndrome, acute myelogenous leukemia or multiple myeloma, or the Field, in accordance with an agreed-upon budget and milestones, which we call the research program. The LLS Agreement initially required us to perform the development activities on a compound that we are no longer developing. We and LLS amended the LLS Agreement in April 2013 to allow us to propose alternative compounds to LLS and for LLS to decide whether it would fund the research program for an alternative compound. We proposed CPI-0610, and LLS agreed to fund CPI-0610 as the alternative compound in June 2013. We and LLS further amended the LLS Agreement in June 2013, June 2014 and March 2016 to reflect changes to the research program milestones.

LLS has agreed to pay us up to $7.5 million, or the LLS Funding, toward the costs of the research program. We may use such funding solely to pay or reimburse expenses of the research program in accordance with an agreed-upon budget. As of December 31, 2018, LLS has paid us $7.3 million in aggregate, and no additional funding paid in the year ended December 31, 2019. We are obligated, and have to date provided funding, to match LLS's funding to support the research program.

We are obligated to use commercially reasonable efforts to conduct the research program substantially in accordance with an agreed-upon research plan with the goal of developing an LLS Product for commercial sale. Once the research program is complete, we are obligated to use, at our own expense, commercially reasonable efforts to develop at least one LLS Product in the Field in the United States, France, Germany, Italy, Spain, the United Kingdom or Japan, or the major market countries, and, following receipt of regulatory approval for at least one LLS Product in any major market country, to commercialize the LLS Product in the Field in such country. If we fail to meet the foregoing obligation, then, under certain circumstances, LLS may terminate the agreement and LLS may exercise the exclusive, sublicensable, worldwide license we granted LLS in certain of our intellectual property to develop and commercialize CPI-0610.

We are obligated to pay to LLS up to $25 million, which would be payable in variable portions based on our execution of any agreement to license or permanently transfer rights to CPI-0610 or an LLS Product to an unaffiliated third party, on the closing of a change of control of our company, or on the receipt of regulatory approval in certain of the major market countries, which we refer to as the Payment Cap Payments. Our payment obligations to LLS continue until satisfied and otherwise only terminate upon a termination of the LLS Agreement by us in the event of a material breach by LLS. The LLS Agreement expires when there are no longer any payment obligations owing from one party to the other with respect to any of these provisions.

We and LLS may terminate the LLS agreement for a material breach by the other party that is not cured within a specified period. LLS may terminate the LLS Agreement if we are debarred by the FDA or excluded from health care programs, or if we knowingly use for any services under the LLS Agreement any individual or entity who is debarred or excluded, or if we undergo certain bankruptcy events. If LLS terminates the LLS Agreement because we are debarred by the FDA or excluded from health care programs, or knowingly use the services of any individual or entity who is debarred or excluded for any services under the LLS Agreement, or we materially breach the LLS Agreement and do not cure within the specified time period, we are obligated to repay LLS the LLS Funding and, if we continue development of the LLS Product thereafter, we also must pay LLS the Payment Cap Payments.

Government Regulation and Product Approvals

Government authorities in the United States at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed

with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal investigations and penalties brought by the FDA or Department of Justice, or DOJ, or other government entities, including state agencies.

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage, including *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity and long-term toxicity studies may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial, and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day

waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In these cases, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls (CMC). A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol may not be allowed to proceed, while other protocols may be allowed. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, a clinical trial may only resume after the FDA has so notified the sponsor. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the clinical trial can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or the competitive environment.

Information about clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website. Similar requirements for posting clinical trial information are present in the European Union (EudraCT) website: https://eudract.ema.europa.eu/ and other countries, as well.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

On December 13, 2016, the 21st Century Cures Act established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug. Such Phase 3 studies are referred to as "pivotal."

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under Accelerated Approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case 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, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies. They 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, purity and potency of the final drug. 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.

Pediatric Studies

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

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety, purity and potency of the proposed drug product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical 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 independent investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, purity and potency of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new non-biologic drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Biologic Licensing Applications, of BLAs, are submitted for approval of biologic products. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2020 is $2,943,965 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2020 is $325,424. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation, an exception from the program fee when the program does not engage in manufacturing the drug during a particular fiscal year and a waiver for certain small businesses.

The FDA conducts a preliminary review of the application, generally within 60 calendar days of its receipt, and strives to inform the sponsor within 74 days whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for Priority Review are meant to be reviewed within six months of the filing date. For applications seeking approval of products that are not NMEs, the ten-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act, or PDUFA, goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is being or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. A REMS uses risk-minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, the seriousness of the disease, the expected benefit of the product, the expected duration of treatment, the seriousness of known or potential adverse events and whether the product is a new molecular entity.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that review, evaluate and provide 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 the FDA considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Regenerative Advanced Therapy designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interaction with the FDA, and the FDA may initiate review of sections of a Fast Track product’s application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information, and the sponsor must pay applicable user fees. However, the FDA’s time-period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for Priority Review if it treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A Priority Review designation is intended to direct overall attention and resources to the evaluation of such applications and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

With passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as Regenerative Advanced Therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and if preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of a Regenerative Advanced Therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for Priority Review and Accelerated Approval based on surrogate or intermediate endpoints.

Accelerated Approval Pathway

The FDA may grant Accelerated Approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant Accelerated Approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted Accelerated Approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of Accelerated Approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with Accelerated Approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support Accelerated Approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The Accelerated Approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, Accelerated Approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of Accelerated Approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with Priority Review.

The Accelerated Approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

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

If the FDA approves a new product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, or require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including a REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS programs can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. The FDA may require a REMS before or after approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product. After approval, many types of changes to the approved product, such as adding new indications, changing manufacturing processes and adding labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors 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 ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit to the FDA samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

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

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;

- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drug samples at the federal level and set minimum standards for the regulation of distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Section 505(b)(2) NDAs

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

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

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an Abbreviated New Drug Application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are abbreviated because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, route of administration, dosage form, strength and conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is bioequivalent to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or the patient.

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

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

The FDA must establish a Priority Review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The FDA is also authorized to expedite review of "competitor generic therapies" or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

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

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

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

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, the expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

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

Pediatric Exclusivity

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

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the

remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and only those claims covering the approved product, a method for using it, or a method for manufacturing it may be extended. Additionally, the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

FDA Approval of Companion Diagnostics

If safe and effective use of a therapeutic depends on an in vitro diagnostic, then the FDA generally will require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, if FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of in vitro companion diagnostics in conjunction with the review of our therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

The FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, for federal fiscal year 2020, the standard fee is $340,995 and the small business fee is $85,249.

A clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

Health Care Law and Regulation

Health care providers and third-party payers play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payers and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or 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 created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;
- the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as 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 health care items or services that are reimbursed by non-government third-party payers, including private insurers.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Health Care Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payers to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payers, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for, the product. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the product once coverage is approved. Third-party payers are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payers may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payer not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payer's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payer's determination to provide coverage for a product does not assure that other payers will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payer to payer.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the health care system in the United States.

In March 2010, the United States Congress enacted the Patient Protection and Affordable Care Act, or ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% (and 70% starting January 1, 2019) point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President 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.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. 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 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, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs 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 or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates 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. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them, which is under review in the U.S. Supreme Court during its current term. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

In addition, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. For example, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

For example, on May 11, 2018, the Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services (HHS) will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program;

update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and 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, which could result in reduced demand for our product candidates or additional pricing pressures.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others. Specifically, however, the process governing approval of medicinal products in the European Union, or EU, generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on GCP and the related national implementing provisions of the individual member states of the European Union, or EU Member States, govern the system for the approval of clinical trials in the EU. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014, was adopted. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial. As of January 1, 2020, the website of the European Commission reported that the implementation of the Clinical Trials Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit, and that the new legislation would come into effect six months after the European Commission publishes a notice of this confirmation. The website indicated that the audit was expected to commence in December 2020.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Concerned Member States). Part II is assessed separately by each Concerned Member State. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the Concerned Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

PRIME Designation in the EU

In March 2016, the European Medicines Agency, or EMA, launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies, or CAT, are appointed early in PRIME scheme facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved Paediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e. the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the applicant also be used in certain other cases. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is responsible for conducting the initial assessment of a product and for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU Member States and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may grant a so-called “marketing authorization under exceptional circumstances”. Such authorization is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

A marketing authorization under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment and a negative assessment could potentially result in the marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional circumstances, however, follows the same rules as a “normal” marketing authorization. Thus, a marketing authorization under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal.

The European Commission may also grant a so-called “conditional marketing authorization” prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

The EU medicines rules expressly permit the EU Member States to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU Member States may prohibit or restrict us from commercializing our products, even if they have been granted an EU marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Paediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the European Union, applicants must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate, or SPC.

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU Member States and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the 10-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements After a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.
- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the United Kingdom and the European Union have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the United Kingdom will not seek to extend the transitional period beyond the end of 2020. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic disruption. The Prime Minister has also indicated that the UK will not accept high regulatory alignment with the EU.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation (GDPR), which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards

to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, EU Member States have the option to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced EU Member States, can further reduce prices. 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 products, if approved in those countries.

Employees

As of February 29, 2020, we had 106 full-time employees, including a total of 41 employees with M.D. or Ph.D. degrees. Of these full-time employees, 81 employees were engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Facilities

We currently occupy approximately 47,546 square feet of office space in Cambridge, Massachusetts under a lease that expires in June 2023.

Scientific Advisory Board

We have established a scientific advisory board and we regularly seek advice and input from these leading scientists and physicians on matters related to our research and development programs. The members of our advisory board consist of experts across a range of key disciplines relevant to our programs. Our advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. In addition, our advisors may have arrangements with other companies to assist those companies in developing products or technologies that may compete with ours. All of our advisors are affiliated with other entities and devote only a small portion of their time to us. The current members of our scientific advisory board are:

Name	Positions
David Livingston, M.D.	Deputy Director, Dana Farber Harvard Cancer Center and Professor of Medicine and Genetics, Harvard Medical School
Scott Lowe, Ph.D.	Chair of the Geoffrey Beene Cancer Research Center, Cancer Biology and Genetics Program, Sloan-Kettering Institute and Howard Hughes Medical Institute
Robert Schreiber, Ph.D.	Professor of Pathology and Immunology, Professor Molecular Microbiology and Director of the Center of Human Immunology and Immunotherapy programs, Washington University School of Medicine
Padmanee Sharma, M.D., Ph.D.	Professor, Department of Genitourinary Medical Oncology, Department of Immunology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

ADDITIONAL INFORMATION

We were incorporated as a Delaware corporation in 2008. Our principal executive offices are located at 215 First Street, Suite 200, Cambridge, Massachusetts 02142, and our telephone number is (617) 714-0555. Our wholly owned subsidiary is Constellation Securities Corporation.

Our Internet address is *www.constellationpharma.com*. Through a link on the "Investor Relations" section of this website, *ir.constellationpharma.com*, we make available, free of charge, our annual report on Form 10-K, quarterly reports on Form 10-Q, proxy statement on Form DEF 14A, current reports on Form 8-K, and any amendments to those 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, we will provide electronic or paper copies of our filings free of charge upon request. Information contained on our corporate website or any other website is not incorporated into this Annual Report and does not constitute a part of this Annual Report.

The SEC also maintains a website containing reports, proxy materials and information statements, among other information, at *http://www.sec.gov*.

Item 1A. Risk Factors.

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

Risks related to our financial position and need for additional capital

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $85.6 million for the year ended December 31, 2019, $59.9 million for the year ended December 31, 2018 and $35.4 million for the year ended December 31, 2017. As of December 31, 2019, we had an accumulated deficit of $319.4 million. To date, we have financed our operations primarily though sales of convertible preferred stock, payments received in connection with collaboration agreements, borrowings under loan agreements and proceeds from our public and private offerings of our common stock. All of our revenue to date has been collaboration revenue. We have devoted substantially all of our financial resources and efforts to research and development, including clinical trials and preclinical studies. We are still in the early stages of development of our product candidates, and we have not completed development of any product candidates. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we continue to advance our goal to become a late-stage oncology development company, including:

- continue our Phase 1b/2 clinical trial of CPI-1205, which we refer to as the ProSTAR trial, our Phase 2 clinical trial of CPI-0610, which we refer to as MANIFEST, and our Phase 1/2 clinical trial of CPI-0209, our second-generation EZH2 inhibitor;
- advance our clinical-stage product candidates into later stage trials, including our plans to conduct a Phase 3 trial of CPI-0610;
- continue the research and development of our other product candidates;
- seek to discover and develop additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval;
- scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;
- acquire or in-license products, product candidates or technologies;
- maintain, expand, enforce, defend and protect our intellectual property portfolio;
- hire additional personnel to support our product development and planned future commercialization efforts and our operations as a public company.
- add operational, financial and administrative personnel, including personnel to support our product development and planned future commercialization efforts and our operations as a public company.

To become and remain profitable, we must succeed in developing, and eventually commercializing, a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses will increase if, among other things:

- we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform trials or studies in addition to those currently expected;
- there are any delays in completing our clinical trials or the development of any of our product candidates; or
- there are any third-party challenges to our intellectual property or we need to defend against any intellectual property-related claim.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

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

We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we continue our Phase 1b/2 clinical trial of CPI-1205, our Phase 2 clinical trial of CPI-0610, and our Phase 1/2 clinical trial of CPI-0209 and plan a Phase 3 clinical trial of CPI-0610; and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these and other product candidates. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our preclinical activities and clinical trials. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we will incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the progress, costs and results of our ongoing Phase 1b/2 clinical trial of CPI-1205, Phase 2 clinical trial of CPI-0610, Phase 1/2 clinical trial of CPI-0209 and the planned Phase 3 clinical trial of CPI-0610;
- the scope, progress, results and costs of discovery research, preclinical development, laboratory testing and clinical trials for any other product candidates we may develop in the future;
- the number and development requirements of other product candidates that we pursue;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- milestones and other collaboration-based revenues, if any;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our 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 and proprietary rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other products, product candidates or technologies.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of approximately $383.9 million. We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2019, will enable us to fund our planned operating expenses and capital expenditure requirements into the second half of 2022. However, we have based these estimates on assumptions that may prove to be wrong, and our operating plan may change as a result of many factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Commercial revenues, if any, will not be derived unless and until we can achieve sales of commercially available products, which we do not anticipate for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our product candidates or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses 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 or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in early 2008, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. All but two of our product candidates are still in preclinical development. We have not yet demonstrated our ability to successfully develop any product candidate, obtain regulatory approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions our stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as our business grows, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, our stockholders should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

If we fail to comply with the covenants or payment obligations under our debt instrument, this could result in an event of default , which could materially and adversely affect our business and our financial condition.

On March 20, 2019, we entered into a Loan and Security Agreement, or the Loan Agreement, with various lenders and Hercules Capital, Inc. pursuant to which we have borrowed $30.0 million to date and $10.0 million remains available to us, subject to certain time limitations, achievement of performance milestones and lender approval. The term loan bears interest at an annual rate equal to the greater of 8.55% and the prime rate of interest plus 2.55%. The Loan Agreement provides for interest-only payments until April 30, 2021, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on May 1, 2021 and continuing through April 1, 2023, or the Maturity Date. In addition, we are required to pay a fee of 6.35% of the aggregate amount of advances under the Loan Agreement at maturity. At our option, we may elect to prepay all or a portion of the outstanding advances by paying the entire principal balance (or such portion thereof) and all accrued and unpaid interest thereon plus a prepayment charge equal to the following percentage of the principal amount being prepaid: 2% if an advance is prepaid during the first 12 months following the applicable advance date, 1% if an advance is prepaid after 12 months but prior to 24 months following the applicable advance date, and 0.5% if an advance is prepaid any time after 24 months following the applicable advance date but prior to the Maturity Date. In connection with the Loan Agreement, we granted Hercules Capital, Inc. a security interest in all of our personal property now owned or hereafter acquired, excluding intellectual property (but including the rights to payment and proceeds from the sale, licensing or disposition of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants. If we fail to make payments when due, or breach any operational covenant or have any event of default, this could have a material adverse effect on our business and financial condition.

Our existing and future indebtedness may limit cash flow available to invest in the ongoing needs of our business.

As of December 31, 2019, we had $30.0 million of borrowings outstanding under the Loan Agreement with Hercules Capital, Inc. $10.0 million remains available for borrowing under the Loan Agreement, subject to certain conditions. We could in the future incur additional indebtedness under the Hercules Loan Agreement or via future loan agreements.

Our debt combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

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

We intend to satisfy our current and future debt service obligations with our existing cash and funds from external sources. Nonetheless, we may not have sufficient funds or may be unable to arrange for additional financing to pay the amounts due under our existing or any future debt. Funds from external sources may not be available on acceptable terms, if at all. In addition, a failure to comply with the covenants under the Hercules Loan Agreement or any future loan agreements we may enter into could result in an event of default and acceleration of amounts due. If an event of default occurs and the lenders accelerate the amounts due under such loan agreements, we may not be able to make accelerated payments, and such lenders could seek to enforce security interests in the collateral securing such indebtedness.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, the U.S. government enacted the Tax Cuts and Jobs Act, or TCJA, which significantly reforms the Internal Revenue Code of 1986, as amended. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be

carried forward indefinitely), one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the TCJA. The impact of this reform on holders of our common stock is also uncertain and could be adverse. We urge investors in our common stock to consult with their legal and tax advisors with respect to TCJA and the potential tax consequences of investing in or holding our common stock.

Risks Related to the Discovery and Development of our Product Candidates

Our approach to the discovery and development of product candidates based on the inhibition of epigenetic regulators by small molecules is an emerging field, and we do not know whether we will be able to successfully develop any products.

The discovery and development of small molecules that inhibit epigenetic regulators to restore normal gene expression is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. Although epigenetic regulation of gene expression plays an essential role in biological function, few drugs premised on the inhibition of epigenetic regulators have been developed.

Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must conduct extensive clinical trials to demonstrate the safety and efficacy of such product candidate in humans. We have not yet begun or completed a pivotal clinical trial of any product candidate. Clinical trials may fail to demonstrate that our product candidates are safe for humans and effective for indicated uses. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may cause delays in the approval or rejection of an application. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our epigenetic platform, or any similar or competitive epigenetic platforms, will result in the development and regulatory approval of any products. There can be no assurance that any development problems we experience in the future related to our epigenetics platform or any of our research programs will not cause significant delays or unanticipated costs, or that such development problems can be solved.

In addition, adverse developments in preclinical studies or clinical trials conducted by others of epigenetic product candidates or adverse events in patients treated with epigenetic products may cause the FDA or other regulatory agencies to require modifications to clinical trials of epigenetic product candidates, revise the requirements for approval of epigenetic product candidates or limit the use of epigenetic products, any of which could materially harm our business. Moreover, there have been significant adverse side effects in clinical trials of epigenetic product candidates of our competitors. For example, , one such competitor reported that some patients in its Phase 1 clinical trial of an EZH2 inhibitor had developed secondary malignancies following treatment. This same company previously reported that in the course of the preclinical safety studies of its EZH2 inhibitor it had observed the development of lymphoma in rats. We have no clinical data from our studies to date to suggest that patients are likely to experience similar side effects with our product candidates that inhibit EZH2. However, due to concerns regarding hematological malignancies, the FDA previously inquired about our plans for typical long-term toxicology studies of CPI-1205, and required that we include the development of a rare leukemia as a potential risk in the informed consent for our CPI-1205 and CPI-0209 trials. The FDA required us to update the investigator's brochure and informed consent for our trials of CPI-1205 and the investigator's brochure and the study protocol for CPI-0209 to include the risk of the development of T-cell lymphoma. The FDA provided guidance regarding our planned long-term toxicology study in rats, including that it should be designed to enhance the probability of detecting whether the development of lymphoma is associated with exposure to these product candidates. On October 4, 2019 we received reports from the 90-day repeat-dose toxicology study indicating once daily oral administration of CPI-1205 in the main study group rats resulted in malignant lymphoma in four out of ten female rats in the high dose (300 mg/kg/day) group. This finding was not observed in male rats. Although lymphoma can occur spontaneously in young rats, these findings were considered related to administration of CPI-1205 due to the high incidence in the females at 300 mg/kg/day relative to controls. As of May 17, 2019, a total of 116 patients have been treated with CPI-1205 in clinical trials. Based on a review of all treatment-emergent adverse events reported by 116 patients as of May 17, 2019, there have been no findings of secondary malignancies or premalignant conditions. We have notified the FDA of these preclinical toxicology findings and have updated our investigator brochure and informed consent form for CPI-1205 to include information about the findings of the toxicology study.

Adverse events in our or our competitors' preclinical studies and/or clinical trials of epigenetic product candidates, even if not ultimately attributable to the product candidate under exploration, and the resulting negative publicity, could result in increased governmental regulation, unfavorable public perception, inadequate acceptance in the medical community, potential regulatory delays in the testing or approval of our product candidates and any additional product candidates that we may identify and develop, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product candidates.

Any of these factors may prevent us from completing our preclinical studies, completing any clinical trials that we may initiate or commercializing any product candidates we may develop, on a timely or profitable basis, if at all.

We are early in our development efforts. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts. We currently have three product candidates in clinical trials that we are developing, CPI-0610 for the treatment of myelofibrosis, or MF, CPI-1205 for the treatment of metastatic castration-resistant prostate cancer, or mCRPC, and a recently initiated Phase 1/2 clinical trial for our second generation EZH2 inhibitor CPI-0209. All of our other product candidates are still in preclinical development. We have invested substantially all of our efforts and financial resources in our integrated epigenetics platform to discover and develop new drugs that selectively modulate gene expression that may lead to the killing or reprogramming of cancer cells or result in anti-tumor immune activity. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- successfully completing preclinical studies and clinical trials;
- expanding and maintaining a workforce of experienced scientists and others with relevant experience to continue to develop our product candidates;
- successfully applying for and receiving marketing approvals from applicable regulatory authorities;
- obtaining and maintaining intellectual property protection and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- establishing sales, marketing and distribution capabilities and successfully launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of the products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining coverage, adequate pricing and adequate reimbursement from third-party payors, including government payors;
- maintaining, enforcing, defending and protecting our rights in our intellectual property portfolio;
- not infringing, misappropriating or otherwise violating others' intellectual property or proprietary rights; and
- maintaining a continued acceptable safety profile of the products following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully develop and commercialize our product candidates, which would materially harm our business.

We may not be successful in our efforts to use our product platform to build a pipeline of product candidates.

One element of our strategy to date has been to use our integrated epigenetics product platform to build a pipeline of small molecule product candidates that selectively modulate gene expression in tumor and immune cells to drive anti-tumor activity and progress these product candidates through clinical development for the treatment of a variety of different types of cancer.

We may not be able to identify additional compelling potential product candidates. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our technological approach, we will not be able to obtain product revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We have product candidates in clinical development and preclinical development. The risk of failure for each of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans.

Product candidates are subject to continued preclinical safety studies, which may be conducted concurrent with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Furthermore, the failure of any of our product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of our other product candidates and/or cause the FDA or other regulatory authorities to require additional testing before approving any of our product candidates. In addition, results from compassionate use protocols or investigator-sponsored trials may not be confirmed in company-sponsored trials and/or may negatively impact the prospects for our programs.

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

- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- we may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful;
- preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- regulators or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- clinical or regulatory developments with competitive product candidates could impact our clinical trial enrollment and/or requirements, costs and timelines for potential approval of our own product candidates;
- regulators or IRBs may require us to perform additional or unanticipated clinical trials to obtain approval or we may be subject to additional post-marketing testing requirements to maintain regulatory approval;

- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be delayed, insufficient or inadequate;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs to suspend or terminate the trials; and
- regulators may withdraw their approval of a product or impose restrictions on its distribution, such as in the form of a risk evaluation and mitigation strategy, or REMS.

We may use new or novel endpoints or methodologies and the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results. Even if applicable regulatory authorities do not object to our proposed endpoints in an earlier stage clinical trial, such regulatory authorities may require evaluation of additional or different clinical endpoints in later-stage clinical trials. Even if the FDA does find our clinical trial success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance in any pivotal or other clinical trials we may conduct for our product candidates. Further, even if we do achieve the pre-specified criteria, our trials may produce results that are unpredictable or inconsistent with the results of the more traditional efficacy endpoints in the trial. The FDA also could give overriding weight to other efficacy endpoints over a primary endpoint, even if we achieve statistically significant results on that primary endpoint, if we do not do so on our secondary efficacy endpoints. The FDA also weighs the benefits of a product against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of approval. Other regulatory authorities in Europe and other countries may make similar findings with respect to these endpoints.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

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

Our product development costs will also increase if we experience delays in testing or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. We may also determine to change the design or protocol of one or more of our clinical trials, including to add additional arms or patient populations, which could result in increased costs and expenses and/or delays. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. In particular, because certain of our products may be focused on specific patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for product candidates that may treat the broader patient populations within which our product candidates are being developed for the treatment of a subset of identifiable patients with cancer and other diseases, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Patient enrollment is affected by a variety of other factors, including:

- the prevalence and severity of the disease under investigation;
- the eligibility criteria for the trial in question;
- the perceived risks and benefits of the product candidate under trial;
- the existence of existing treatments for the indications for which we are conducting clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients;
- the conducting of clinical trials by competitors for product candidates that treat the same indications as our product candidates;
- the ability to identify specific patient population for biomarker-defined trial cohort(s); and
- the cost to, or lack of adequate compensation for, prospective patients.

Our inability to locate and enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse events or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

If our product candidates, either alone or in combination with other therapeutics, are associated with serious adverse events or undesirable side effects in clinical trials or have characteristics that are unexpected in clinical trials or preclinical testing, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In pharmaceutical development, many compounds that initially show promise in early-stage or clinical testing for treating cancer are later found to cause side effects that prevent further development of the compound. In addition, if third parties manufacture or use our product candidates without our permission, and generate adverse events or unacceptable side effects, this could also have an adverse impact on our development efforts.

We are currently pursuing the development of our product candidates in combination with other approved therapeutics. If the FDA revokes approval of any such therapeutic, or if safety, efficacy, manufacturing or supply issues arise with any therapeutic that we use in combination with one of our product candidates in the future, we may be unable to further develop and/or market our product candidate or we may experience significant regulatory delays or supply shortages, and our business could be materially harmed.

We are pursuing the development of our product candidates in combination with other approved therapeutics. We are currently conducting (i) a Phase 1b/2 clinical trial of CPI-1205 for the treatment of mCRPC in combination with enzalutamide, which is marketed by Pfizer Inc. and Astellas Pharma Inc. and is currently approved to treat mCRPC, or abiraterone acetate, which is marketed by Janssen and is currently approved for use in combination with prednisone for the treatment of patients with mCRPC, and (ii) a Phase 2 clinical trial of CPI-0610 as a monotherapy or in combination with ruxolitinib, which is marketed by Incyte, Inc. and is currently approved to treat intermediate or high-risk MF. We may commence additional clinical trials of our product candidates in combination with other approved therapeutics, including, if our Phase 1b/2 trial is successful, a pivotal clinical trial of CPI-1205 in combination with either enzalutamide or abiraterone acetate for the treatment of mCRPC. We may also seek to develop our product candidates in combination with other therapeutics in the future.

We did not develop or obtain regulatory approval for, and we do not manufacture or sell, any of these approved therapeutics. In addition, these combinations have not been tested before and may, among other things, fail to demonstrate synergistic activity, may fail to achieve superior outcomes relative to the use of single agents or other combination therapies, may exacerbate adverse events associated with one of our product candidates when used as monotherapy or may fail to demonstrate sufficient safety or efficacy traits in clinical trials to enable us to complete those clinical trials or obtain marketing approval for the combination therapy.

If the FDA revokes its approval of any of these therapeutics, we will not be able to continue clinical development of or market CPI-1205, CPI-0610 or any other product candidate in combination with such revoked therapeutic. If safety or efficacy issues arise with these or any other therapeutics that we seek to combine with our product candidates in the future, we may experience significant regulatory delays, and the FDA may require us to redesign or terminate the applicable clinical trials. Moreover, if these therapeutics were to receive regulatory approval in combination with a different therapeutic in any indication for which we are pursuing approval, such approval could impact the feasibility and design of any subsequent clinical trials that we may seek to conduct evaluating CPI-1205, CPI-0610 or any other product candidate in combination with such therapeutic. If manufacturing, cost or other issues result in a supply shortage of these therapeutics or any other combination therapeutics, we may not be able to complete clinical development of CPI-1205 or CPI-0610 on our current timeline or at all, or any other product candidate we may develop in the future.

In addition, we may need, for supply, data referencing or other purposes, to collaborate or otherwise engage with the companies who market these approved therapeutics. If we are unable to do so on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate or indication, reduce or delay its development program, delay its potential commercialization or reduce the scope of any sales or marketing activities.

Even if CPI-1205, or CPI-0610, or any other product candidate were to receive regulatory approval and be commercialized for use in combination with enzalutamide, abiraterone acetate, ipilimumab, pembrolizumab or ruxolitinib, as applicable, or another therapeutic, we would continue to be subject to the risk that the FDA could revoke its approval of such therapeutic, that safety, efficacy, manufacturing, cost or supply issues could arise with one of these therapeutic agents, or that the current standard of care may be replaced. This could result in CPI-1205, CPI-0610 or any such other product candidate, if approved, being removed from the market or being less successful commercially.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. For example, we made a strategic decision to advance development of CPI-1205 in solid tumors, despite encouraging clinical data in our Phase 1 trial of CPI-1205 in patients with progressive/relapsed lymphoma, primarily due to strategic considerations with respect to a pathway to regulatory approval and potential commercial opportunities. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We currently conduct clinical trials for product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We currently conduct clinical trials outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and be performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and could delay or permanently halt our development of the applicable product candidates.

Risks Related to the Commercialization of Our Product Candidates

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

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages of our product candidates compared to alternative treatments;
- our ability to offer our products for sale at competitive prices;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products together with other medications.

Our assessment of the potential market opportunity for our product candidates is based on industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for any of our product candidates may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

In the future, we expect to build a focused, specialty sales and marketing infrastructure to market some of our product candidates in the United States, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Specifically, there are a large number of companies developing or marketing treatments for cancer, including many large pharmaceutical and biotechnology companies. In addition, many companies are developing cancer therapies that work by targeting epigenetic mechanisms, including through EZH2 and BET inhibition, such as AbbVie Inc., AstraZeneca PLC, BMS, CellCentric Ltd, Daiichi Sankyo Company, Eli Lilly & Company, Epizyme, Inc., GlaxoSmithKline plc, Incyte, Inc., Novartis AG, Pfizer Inc. and Zenith Epigenetics Ltd.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products before we do, or that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in additional challenges to our regulatory approval strategy and/or our competitors establishing a stronger market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. Generic products are currently on the market for many of the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do.

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

If our contracted manufacturing facilities experience production issues for any reason, and/or we experience import/export issues for any reason, we may be unable to manufacture or supply clinical supplies or commercial quantities of our product candidates for a substantial amount of time, which could have a material adverse effect on our business.

We rely, and expect to continue to rely, on third parties to manufacture clinical supplies of our product candidates and commercial supplies of our products, if and when approved for marketing by applicable regulatory authorities, as well as for packaging, sterilization, storage, distribution and other production logistics. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, if there are disagreements between us and such parties, or if such parties are unable to expand capacities to support commercialization of any of our product candidates for which we obtain marketing approval, we may not be able to fulfill, or may be delayed in producing sufficient product candidates to meet, our supply requirements.

Similarly, we previously reported that we were closely monitoring our CPI-0610 supply due to potential production shortages with one of our manufacturers. In addition, the various manufacturing facilities with which we do business may also be affected by natural disasters, such as floods or fire, or societal disruptions or outbreaks such as the recently identified coronavirus. Further, facilities could face manufacturing issues, such as contamination or regulatory concerns following a regulatory inspection of such facility. In such instances, we may need to locate an appropriate replacement third-party facility and establish a contractual relationship, which may not be readily available or on acceptable terms, which would cause additional delay and increased expense, including as a result of additional required FDA approvals, and may have a material adverse effect on our business.

Our third-party manufacturers are subject to inspection and approval by the FDA before we can commence the manufacture and sale of any of our product candidates, and thereafter subject to FDA inspection from time to time. Failure by our third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses.

We or our third-party manufacturers may also encounter shortages in the raw materials or active pharmaceutical ingredient necessary to produce our product candidates in the quantities needed for our clinical trials or, if our product candidates are approved, in sufficient quantities for commercialization or to meet an increase in demand, as a result of capacity constraints or delays or disruptions in the market for the raw materials or active pharmaceutical ingredient, including shortages caused by the purchase of such raw materials or active pharmaceutical ingredient by our competitors or others. The failure of us or our third-party manufacturers to obtain the raw materials or active pharmaceutical ingredient necessary to manufacture sufficient quantities of our product candidates, may have a material adverse effect on our business.

Some of our manufacturing activities take place outside of the United States. In addition, with respect to clinical trial or manufacturing activities that take place outside of the United States, changes in import/export regulations or practices could impact our ability to obtain critical materials, drug substance, or product candidates across international borders. Such challenges could have a material adverse effect on our business.

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of

reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

There can be no assurance that our product candidates, even if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payors, or that coverage and an adequate level of reimbursement will be available or that third-party payors' reimbursement policies will not adversely affect our ability to sell our product candidates profitably.

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

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and use of our product candidates through compassionate use, and we will face an even greater risk if we commercially sell any products that we may develop. For example, on January 17, 2017, a participant dosed in one of the Company's clinical trials filed a complaint against us in the United States District Court for the District of Arizona, alleging negligence, lack of informed consent, strict products liability and loss of consortium. The parties have reached agreement with regards to a resolution.

If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

We currently hold $10 million in product liability insurance coverage in the aggregate, with a per incident limit of $10 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. 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.

Risks Related to Our Dependence on Third Parties

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely on third-party clinical research organizations to conduct our ongoing Phase 1b/2 clinical trial of CPI-1205, our Phase 2 clinical trial of CPI-0610 and our Phase 1/2 clinical trial of CPI-0209, and we anticipate we would rely on third-party clinical research organizations or third-party research collaboratives to conduct future clinical trials. We expect to continue to rely on third parties, such as clinical research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities might be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors.

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

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

We do not have any manufacturing facilities, and we rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We also expect to rely on third-party manufacturers or third-party collaborators for the manufacture of commercial supply of any other product candidates for which we or our collaborators obtain marketing approval. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside of the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. In addition, we do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers or sources of drug substance cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

We face risks related to health epidemics and other widespread outbreaks of contagious disease, including the novel coronavirus, COVID-19, which could significantly disrupt our operations and impact our financial results.

Significant outbreaks of contagious diseases, and other adverse public health developments, could have a material impact on our business operations and operating results. In December 2019, an outbreak of respiratory illness caused by a strain of novel coronavirus, COVID-19, began in China. As of March 2020, that outbreak has led to numerous confirmed cases worldwide, including in the Unites States and other countries where we are conducting clinical trials or activities in support thereof. The World Health Organization declared the outbreak a global public health emergency on January 30, 2020. In addition to those who have been directly affected, millions more have been affected by governmental efforts around the world to slow the spread of the outbreak. The outbreak and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce. The future progression of the outbreak and its effects on our business and operations are uncertain.

We and our third-party contract manufacturers, contract research organizations and clinical sites may experience disruptions in supply of product candidates and/or procuring items that are essential for our research and development activities, including, for example, raw materials used in the manufacturing of our product candidates, medical and laboratory supplies used in our clinical trials or preclinical studies or animals that are used for preclinical testing, in each case, for which there may be shortages because of ongoing efforts to address the outbreak. While we believe that we currently have sufficient supply of our product candidates to continue our on-going clinical trials, some of our product candidates, or materials contained therein, come from facilities located in areas impacted by COVID-19, such as China. There is no guarantee that the recent COVID-19, or any potential future outbreak would not impact our future supply chain, which could have a material adverse impact on our clinical trial plans and business operations.

Additionally, we have enrolled, and will seek to enroll, cancer patients in our clinical trials at sites located both in the United States and internationally. Some of our clinical trial sites are outside of the United States, including in areas recently noted as being impacted by COVID-19, such as Italy. In the event that clinical trial sites are slowed down or closed to enrollment in our trials, this could have a material adverse impact on our clinical trial plans and timelines. We may face difficulties recruiting or retaining patients in our ongoing and planned clinical trials if patients are affected by the virus or are fearful of visiting or traveling to our clinical trial sites because of the outbreak.

Any negative impact that the outbreak has the ability of our suppliers to provide materials for our product candidates or on recruiting or retaining patients in our clinical trials could cause costly delays to clinical trial activities, which could adversely affect our ability to obtain regulatory approval for and to commercialize our product candidates, increase our operating expenses, and have a material adverse effect on our financial results.

We may enter into collaborations with third parties for the development or commercialization of our product candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates and our business could be adversely affected.

We may utilize collaboration, distribution and other marketing arrangements with third parties to develop and commercialize CPI-0610, CPI-1205 and/or CPI-0209 or any other product candidates for which we obtain marketing approval in markets outside the United States. We also may enter into arrangements with third parties to perform these services in the United States if we do not establish our own sales, marketing and distribution capabilities in the United States for our product candidates or if we determine that such third-party arrangements are otherwise beneficial. We also may seek third-party collaborators for development and commercialization of other product candidates. Our likely collaborators for any sales, marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Collaborations that we enter into may pose a number of risks, including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development of our product candidates or may elect not to continue or renew development programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew commercialization programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates and products if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over intellectual property or proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly obtain, maintain, enforce, defend or protect our intellectual property or proprietary rights or may use our proprietary information in such a way as to potentially lead to disputes or legal proceedings that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. If any collaborations that we enter into do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates. All of the risks relating to product development, regulatory approval and commercialization described herein also apply to the activities of our collaborators.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

If we are not able to establish collaborations, we may have to alter our development and commercialization plans and our business could be adversely affected.

For some of our product candidates, we may decide to collaborate with pharmaceutical or biotechnology companies for the development and potential commercialization of those product candidates. We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical and biotechnology companies that have resulted in a reduced number of potential future collaborators.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform.

If we are required by FDA to develop a companion diagnostic to identify patients who are likely to benefit from a therapeutic product, we will by reliant on third parties to develop a diagnostic and their failure to do so may delay or prevent approval of the therapeutic product.

In July 2014, the FDA issued final guidance that stated that if safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will not approve the therapeutic unless the FDA approves or clears this "*in vitro* companion diagnostic device" at the same time that the FDA approves the therapeutic. We may be required by FDA to develop companion diagnostics to identify patients who are likely to benefit from our therapeutic product candidates. We expect to rely on third parties for much of the development, testing and manufacturing of such diagnostics. We will likely rely on such third parties to also obtain any required regulatory approval for and then commercially supply such diagnostics. We have very limited experience in the development of diagnostics and, even with the help of third parties with greater experience, may fail to obtain the required diagnostic product marketing approval, which could prevent or delay approval of the therapeutic product. Because we expect to rely on third parties for various aspects of the development, testing and manufacture, as well as for regulatory approval for and commercial supply, of our diagnostics, the commercial success of any of our product candidates that require a diagnostic will be tied to and dependent on the continued ability of such third parties to make the diagnostic commercially available on reasonable terms in the relevant geographies.

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to any proprietary technology and product candidates we develop, including CPI-1205, CPI-0610 and CPI-0209. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our technologies and product candidates that are important to our business and by in-licensing intellectual property related to such technologies and product candidates. If we are unable to obtain or maintain patent protection with respect to any proprietary technology or product candidate, our business, financial condition, results of operations and prospects could be materially harmed. In particular, we do not own or in-license any patented intellectual property related to our epigenetics platform. Accordingly, we may not be able to prevent third parties from developing and commercializing a similar platform or technology to compete with us.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, defend or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce and defend the patents, covering technology that we license from third parties. Therefore, these in-licensed patents and applications may not be prepared, filed, prosecuted, maintained, defended and enforced in a manner consistent with the best interests of our business.

Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

The patent position of pharmaceutical and biotechnology companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the scope of patent protection outside of the United States is uncertain and laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. With respect to both owned and in-licensed patent rights, we cannot predict whether the patent applications we and our licensors 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. In addition, 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 published at all. Therefore, neither we nor our licensors can know with certainty whether either we or our licensors were the first to make the inventions claimed in the patents and patent applications we own or in-license now or in the future, or that either we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our owned and in-licensed patent rights are highly uncertain. For example, with respect to CPI-1205, we own three issued U.S. composition of matter patents that contain claims covering CPI-1205 specifically and generically. We are aware of prior art that may invalidate some but not all of the generic claims included in one of the composition of matter patents. While we believe that the specific claims, and the other generic claims, contained in our issued U.S. composition of matter patents provide protection for the composition of matter of CPI-1205 and are not implicated by such prior art, third parties may nevertheless challenge such claims and if such specific claims, or any such other generic claims on which we may rely, are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired.

Moreover, our owned and in-licensed pending and future patent applications may not result in patents being issued which protect our technology and product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents and our ability to obtain, protect, maintain, defend and enforce our patent rights, narrow the scope of our patent protection and, more generally, could affect the value or narrow the scope of our patent rights.

Moreover, we or our licensors may be subject to a third-party reissuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us. 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. Furthermore, such proceedings also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us.

In January 2018, after completing an internal review of our patent portfolio, we submitted a request to the USPTO to reissue one of our U.S. patents covering CPI-1205 in order to correct one structure in the claims. Corresponding requests have been filed for the corresponding Chinese, Eurasian and Colombian patents, all of which have been reissued with the corrected structure. The United States reissue application claiming the corrected structure was granted.

Additionally, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if our owned and in-licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and in-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 in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Furthermore, our competitors may be able to circumvent our owned or in-licensed patents by developing similar or alternative technologies or products in a non-infringing manner. As a result, our owned and in-licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing technology and products similar or identical to any of our technology and product candidates.

Moreover, some of our owned and in-licensed patents and patent applications are, and may in the future be, co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owner of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Furthermore, our owned and in-licensed patents may be subject to a reservation of rights by one or more third parties. For example, the research resulting in certain of our in-licensed patent rights and technology was funded in part by the U.S. government. As a result, the government may have certain rights, such as march-in rights, to such patent rights and technology. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions substantially in the United States. Any exercise by the government of such rights could harm our competitive position, business, financial condition, results of operations, and prospects. In addition, under the Research, Development and Commercialization Agreement, or the LLS Agreement, with The Leukemia & Lymphoma Society, or LLS, we are required to use commercially reasonable efforts to research, develop and commercialize CPI-0610. If we fail to meet the foregoing obligation, then, under certain circumstances, LLS may terminate the LLS Agreement and may exercise the exclusive, sublicensable and worldwide license we granted LLS in and to certain of our intellectual property to develop and commercialize CPI-0610.

If we do not obtain patent term extension for any product candidates we may develop, our business may be materially harmed.

In the United States, depending upon the timing, duration, and specifics of any FDA marketing approval of a product candidate, the patent term of a patent that covers an FDA-approved drug may be eligible for limited patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to an approved drug may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. While, in the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the

length of such extensions. We may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of the relevant patents, or otherwise failing to satisfy applicable requirements. If we are unable to obtain any patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following the expiration of our patent rights, and our business, financial condition, results of operations, and prospects could be materially harmed.

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

Changes in either the patent laws or interpretation of patent laws in the United States, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our owned and in-licensed patent applications and the maintenance, enforcement or defense of our owned and in-licensed issued patents. The Leahy-Smith Act includes a number of significant changes to United States patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

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

Competitors and other third parties may infringe, misappropriate or otherwise violate our or our licensor's issued patents or other intellectual property. As a result, we or our licensors may need to file infringement, misappropriation or other intellectual property related claims, which can be expensive and time-consuming. Any claims we assert against perceived infringers could provoke such parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property. In addition, in a patent infringement proceeding, such parties could counterclaim that the patents we or our licensors have asserted are invalid or unenforceable. In 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, including 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. Third parties may institute such claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings).

An adverse result in any such proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly, and could put any of our owned or in-licensed patent applications at risk of not yielding an issued patent. A court may also refuse to stop the third party from using the technology at issue in a proceeding on the grounds that our owned or in-licensed patents do not cover such technology. 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 or trade secrets could be compromised by disclosure during this type of litigation. Any of the foregoing could allow such third parties to develop and commercialize competing technologies and products and have a material adverse impact on our business, financial condition, results of operations, and prospects.

Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. There is considerable patent and other intellectual property litigation in the pharmaceutical and biotechnology industries. We may become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and product candidates, including interference proceedings, post grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions such as oppositions before the European Patent Office.

The legal threshold for initiating litigation or contested proceedings is low, so that even lawsuits or proceedings with a low probability of success might be initiated and require significant resources to defend. Litigation and contested proceedings can also be expensive and time-consuming, and our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. The risks of being involved in such litigation and proceedings may increase if and as our product candidates near commercialization and as we gain the greater visibility associated with being a public company. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of merit. We may not be aware of all such intellectual property rights potentially relating to our technology and product candidates and their uses. Thus, we do not know with certainty that our technology and product candidates, or our development and commercialization thereof, do not and will not infringe, misappropriate or otherwise violate any third party's intellectual property.

Even if we believe that third party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of misappropriation, infringement, validity, enforceability, or priority. A court of competent jurisdiction could hold these third-party patents are valid, enforceable, and infringed, which could materially and adversely affect our ability to commercialize any technology or product candidate covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our technology and product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us and could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right and could be forced to indemnify our customers or collaborators. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. In addition, we may be forced to redesign our product candidates, seek new regulatory approvals and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations, and prospects.

Intellectual property litigation or other legal proceedings relating to intellectual property could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and 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. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and may also have an advantage in such proceedings due to their more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of intellectual property litigation or other proceedings could compromise our ability to compete in the marketplace.

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

Periodic maintenance, renewal and annuity fees and various other government fees on any issued patent and pending patent application must be paid to the USPTO and foreign patent agencies in several stages or annually over the lifetime of our owned and in-licensed patents and patent applications. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In certain circumstances, we rely on our licensing partners to pay these fees to, or comply with the procedural and documentary rules of, the relevant patent agency. With respect to our patents, we rely on an annuity service to remind us of the due dates and to make payment after we instruct them to do so. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, potential competitors might be able to enter the market with similar or identical products or technology. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, it would have a material adverse effect on our business, financial condition, results of operations, and prospects.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are party to license and funding agreements that impose, and we may enter into additional licensing and funding arrangements with third parties that may impose, diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Under our existing licensing and funding agreements, we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreements. If we fail to comply with such obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements or require us to grant them certain rights. Such an occurrence could materially adversely affect the value of any product candidate being developed under any such agreement. For example, under the LLS Agreement, we are required to use commercially reasonable efforts to research, develop and commercialize CPI-0610. If we fail to meet the foregoing obligation, then, under certain circumstances, LLS may terminate the LLS Agreement and may exercise the exclusive, sublicensable and worldwide license we granted LLS in and to certain of our intellectual property to develop and commercialize CPI-0610. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, which would have a material adverse effect on our business, financial condition, results of operations, and prospects.

Additionally, these and other license agreements may not provide exclusive rights to use the licensed intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products and technology in fields of use and territories not included in such agreements. In addition, we may not have the right to control the preparation, filing, prosecution, maintenance, enforcement, and defense of patents and patent applications covering the technology that we license from third parties. Therefore, we cannot be certain that these patents and patent applications will be prepared, filed, prosecuted, maintained, and defended in a manner consistent with the best interests of our business. If our licensors fail to prosecute, maintain, enforce, and defend such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected.

We may need to obtain additional licenses from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all, or such licenses may be non-exclusive. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all.

If we are unable to obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology and product candidates, which could harm our business, financial condition, results of operations, and prospects significantly.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected technology and product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

Our licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents and patent applications we in-licensed. If other third parties have ownership rights to our in-licensed patents, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize product candidates and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products and technologies identical to ours. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

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

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Consequently, 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 in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection or licenses but enforcement is not as strong as that in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected.

We may be subject to claims by third parties asserting that our employees, consultants, contractors or we have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, consultants and contractors were previously employed at universities or other pharmaceutical or biotechnology companies, including our competitors or potential competitors. Although we try to ensure that our employees and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our intellectual property assignment agreements with them may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive business position and prospects. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

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

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology. 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. Detecting the disclosure or misappropriation of a trade secret and 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 inside and outside of the United States 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 or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- our epigenetics platform is not protected by any patented intellectual property, and we may not be able to develop, acquire or in-license any patentable technologies or other intellectual property related to such platform;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or in-licensed intellectual property rights;
- it is possible that our owned and in-licensed pending patent applications or those we may own or in-license in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside of the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party clinical research organizations or other third-party consultants or vendors to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate’s safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. New cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

We may not be able to obtain orphan drug exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States. For example, in November 2019, we received FDA orphan drug designation for CPI-0610 for the treatment of myelofibrosis.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for that time period. The applicable period is seven years in the United States and ten years in Europe. The exclusivity period in Europe can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug 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 drug to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same 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.

On August 3, 2017, the U.S. Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

A Fast Track designation by the FDA may not lead to a faster development or regulatory review or approval process.

We received Fast Track designation for CPI-0610 for the treatment of myelofibrosis in November 2018 and we may seek Fast Track designation for some of our additional product candidates. If an investigational drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA Fast Track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure stockholders that the FDA would decide to grant it. Even if we do receive Fast Track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program.

A Breakthrough Therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a Breakthrough Therapy designation for some of our product candidates. A Breakthrough Therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive Breakthrough Therapy designation, the receipt of such designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

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

In order to market and sell our products in the European Union and many other foreign jurisdictions, we or our potential third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our potential third-party collaborators may not obtain approvals from regulatory authorities outside of the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in other countries. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the United Kingdom and the European Union have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the United Kingdom will not seek to extend the transitional period beyond the end of 2020. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic disruption. The Prime Minister has also indicated that the UK will not accept high regulatory alignment with the EU.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

If we are required by the FDA to obtain approval of a companion diagnostic in connection with approval of a therapeutic product candidate, and we do not obtain or face delays in obtaining FDA approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. Under the Federal Food, Drug, and Cosmetic Act, or FDCA, companion diagnostics are regulated as medical devices, and the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain Premarket Approval, or a PMA, for the diagnostic. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling.

For example, a clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

Thus, a PMA is not guaranteed and may take considerable time, and the FDA may ultimately respond to a PMA submission with a "not approvable" determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. As a result, if we are required by the FDA to obtain approval of a companion diagnostic for a therapeutic product candidate, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we may not be able to commercialize the product candidate on a timely basis or at all and our ability to generate revenue will be materially impaired.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS. New cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product, including the adoption and implementation of REMS. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

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

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions and warnings on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; or
- litigation involving patients using our products. Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug manufacturers or quality assurance standards applicable to medical device manufacturers, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, any contract manufacturers we may engage in the future, our future collaborators and their contract manufacturers will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to clinicians, recordkeeping, and costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product such as the requirement to implement a REMS.

The efforts of the Trump administration to pursue regulatory reform may limit the FDA's ability to engage in oversight and implementation activities in the normal course, and that could negatively impact our business.

The Trump administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. On January 30, 2017, President Trump issued an executive order, applicable to all executive agencies, including the FDA, requiring that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and on February 2, 2017, the Trump administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security, and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign jurisdictions in which we conduct our business. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at a minimum of $11,181 and a maximum of $22,363 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, 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 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. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government funded healthcare programs.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain for any products that are approved in the United States or foreign jurisdictions.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. The pharmaceutical industry has been a particular focus of these efforts and have been significantly affected by legislative initiatives. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any FDA approved product.

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

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. Among the provisions of the ACA of potential importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any of our product candidates that are approved for sale, are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% starting January 1, 2019) point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2027 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

With enactment of the TCJA, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause an estimated 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump administration has represented to the U.S. Court of Appeals for the Fifth Circuit considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

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 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, among other things, amends the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". Further, each chamber of the U.S. Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs 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 or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates 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. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them, which is under review by the U.S. Supreme Court during its current term. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States, and members of Congress and the Trump administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several recent U.S. congressional inquiries and proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services (HHS) will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and 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, which could result in reduced demand for our product candidates or additional pricing pressures.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. Increased scrutiny by the U.S. 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.

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

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

If we or any third-party manufacturers we engage now or in the future fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs or liabilities that could harm our business.

We and third-party manufacturers we engage now are, and any third-party manufacturers we may engage in the future will be, subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Liability under certain environmental laws governing the release and cleanup of hazardous materials is joint and several and could be imposed without regard to fault. We also could incur significant costs associated with civil or criminal fines and penalties or become subject to injunctions limiting or prohibiting our activities for failure to comply with such laws and regulations.

Although we maintain general liability insurance as well as workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Further, with respect to the operations of our current and any future third-party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products. In addition, our supply chain may be adversely impacted if any of our third party contract manufacturers become subject to injunctions or other sanctions as a result of their non-compliance with environmental, health and safety laws and regulations.

We are subject to anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses, be precluded from developing manufacturing and selling certain products outside the United States or be required to develop and implement costly compliance programs, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or Bribery Act, the U.S. Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that apply in countries where we do business and may do business in the future. The Bribery Act, FCPA and these other laws generally prohibit us, our officers, and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. Compliance with the FCPA, in particular, 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.

We may in the future operate in jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted. If we expand our operations outside of the United States, we will need to dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws. In addition, various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. The Securities and Exchange Commission also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions. Any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, U.S. or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards, 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, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct 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. This could include violations of HIPAA, other U.S. federal and state law, and requirements of non-U.S. jurisdictions, including the European Union Data Protection Directive. It is not always possible to identify and deter employee 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, standards, regulations, guidance or codes of conduct. 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 internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of any collaborators, contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced any such material system failure, accident, cyber-attack or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials 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 were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Risks Related to Employee Matters and Managing Growth

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

We are highly dependent on the research and development, clinical and business expertise of our executive officers, as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment letter agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing, legal and sales and marketing personnel will also be critical to our success. Although we have a robust process for interviewing and hiring personnel, there is no guarantee that individuals will fulfill the obligations we employ them for, or that they will fit within our organizational culture. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Our Common Stock

Our executive officers, directors and entities associated or affiliated with our executive officers and directors, if they choose to act together, have the ability to significantly influence all matters submitted to stockholders for approval.

As of February 29, 2020, our executive officers, directors and entities associated or affiliated with our executive officers and directors, in the aggregate, owned shares representing approximately 10.2% of our capital stock. As a result, if these stockholders were to choose to act together, they could substantially impact matters submitted to our stockholders for approval, as well as our management and affairs.

This concentration of ownership control may:

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

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

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

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

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

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

Our shares of common stock began trading on the Nasdaq Global Select Market on July 19, 2018. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for our stockholders to sell shares without depressing the market price for the shares, or at all.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

The price of our common stock is volatile and fluctuates substantially, which could result in substantial losses for our stockholders

The trading price of our common stock has been, and is likely to continue to be, highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. During the period from July 18, 2018 to March 6, 2020, the closing price of our common stock ranged from a high of $49.30 per share to a low of $4.01 per share. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- results of or developments in clinical trials of our product candidates or those of our competitors;
- our success in commercializing our product candidates, if and when approved;
- the success of competitive products or technologies;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property or proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license products, product candidates or technologies, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

In the past, following periods of volatility in the market price of a company’s securities, securities class-action litigation has often been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management’s attention and resources.

A significant portion of our total outstanding shares are eligible to 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 doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our initial public offering continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

Moreover, holders of a substantial number of shares of our common stock, including shares of our common stock issuable upon exercise of outstanding warrants, have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have filed a registration statement registering all shares of common stock that we may issue under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

On October 3, 2019, we completed a private placement of 7,647,057 shares of our common stock to several accredited investors. In connection with the private placement, we filed a registration statement covering the resale by these investors of the shares of common stock purchased in the private placement, and we agreed to keep the registration statement effective until the date the shares covered by the registration statement have been sold or can be sold without restriction pursuant to Rule 144 of the Securities Act of 1933, as amended.

We currently have on file with the SEC a universal shelf registration statement which allows us to offer and sell registered common stock, preferred stock, debt securities, warrants and/or units from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale. On December 13, 2019, we completed a public offering of 7,475,000 shares of common stock at a public offering price of $34.50 per share. Sales of a substantial number of shares of our common stock, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

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

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an emerging growth company until December 31, 2023, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.07 billion or more in any fiscal year, we would cease to be an emerging growth company as of December 31 of the applicable year. We also would cease to be an emerging growth company if we issue more than $1 billion of non-convertible debt over a three-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may choose to take advantage of some or all of the available exemptions. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

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 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in 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 common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act permits an emerging growth company to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to "opt out" of such extended transition period or (ii) no longer qualify as an emerging growth company.

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

As a public company, we incur, and after we are no longer an emerging growth company we will further incur, significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

We previously identified a material weakness in our disclosure controls and procedures and our internal controls, which we believe has been fully remediated. If we have inadequately remediated this material weakness or if we otherwise fail to develop, implement and maintain appropriate internal controls in future periods, our ability to report our financial condition and results of operations accurately and on a timely basis could be adversely affected.

We previously identified a material weakness in our internal control over financial reporting. The specific material weakness and our remediation efforts are described in Item 9A, “Controls and Procedures” of our Annual Report on Form 10-K for the year ended December 31, 2018, or the Annual Report in “Disclosure Controls and Procedures.” A “material weakness” is a deficiency, or a combination of deficiencies, in internal controls, such that there is a reasonable possibility that a material misstatement of our annual or interim consolidated financial statements would not be prevented or detected. We cannot assure you that additional material weaknesses in our internal controls will not be identified in the future. Any failure to maintain or implement required new or improved controls, or any difficulties we encounter in their implementation, could result in additional material weaknesses, or could result in material misstatements in our financial statements. These misstatements could result in restatements of our financial statements, cause us to fail to meet our reporting obligations or cause investors to lose confidence in our reported financial information.

We have developed certain remediation steps to address the material weakness discussed above and to improve our internal controls. We believe the material weakness discussed above has been fully remediated. If we have inadequately remediated this material weakness, there will continue to be an increased risk that our future financial statements could contain errors that will be undetected. Further and continued determinations that there are material weaknesses in the effectiveness of our internal controls could reduce our ability to obtain financing or could increase the cost of any financing we obtain and require additional expenditures of resources to comply with applicable requirements. For more information relating to our internal controls and disclosure controls and procedures, and the remediation plan undertaken by us, see Item 9A, “Controls and Procedures” of the Annual Report.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be our stockholders’ sole source of gain.

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

Our certificate of incorporation designates the state courts in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the company and our directors, officers and employees.

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, or the DGCL, or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware, or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

We currently occupy approximately 47,546 square feet of office space in Cambridge, Massachusetts under a lease that expires in June 2023. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

At each reporting date, we evaluate whether or not a potential loss amount or a potential range of losses is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. We expense as incurred the costs related to such legal proceedings. On January 17, 2017, a participant dosed in one of the Company’s clinical trials filed a complaint against us in the United States District Court for the District of Arizona, alleging negligence, lack of informed consent, strict products liability and loss of consortium. The parties have reached agreement with regards to a resolution.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock trades under the symbol "CNST" on the Nasdaq Global Select Market and has been publicly traded since July 19, 2018. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of March 6, 2020, there were approximately 78 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

Purchase of Equity Securities

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

Use of Proceeds from Registered Securities

On July 23, 2018 we closed our initial public offering of common stock under a registration statement on Form S-1 (333-225822) that was declared effective by the Securities and Exchange Commission (the "SEC") on July 18, 2018.

We received aggregate net proceeds from the offering of $52.2 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. None of the underwriting discounts and commissions or other offering expenses were incurred or paid to directors or officers of ours or their associates or to persons owning 10% or more of our common stock or to any affiliates of ours.

We have used approximately $10.0 million of the net proceeds from the IPO as of December 31, 2019 to fund the development of CPI-0610, CPI-1205 and CPI-0209, to advance our pipeline of preclinical candidates and to research and develop additional preclinical product candidates using our platform and for working capital and other general corporate purposes. We have invested the unused net proceeds from the offering in money market accounts.

Item 6. Selected Financial Data.

You should read the following selected financial data together with our financial statements and companying notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. We have derived the statement of operations data for the years ended December 31, 2019, 2018, and 2017 and the balance sheet data as of December 31, 2019 and 2018 from our audited financial statements included elsewhere in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of the results that may be expected in any future period.

	Years Ended December 31,		
	2019	2018	2017
	(in thousands, except per share data)		
Consolidated Statement of Operations Data:			
Operating expenses:			
Research and development	$ 66,459	$ 48,769	$ 32,617
General and administrative	19,596	12,475	6,471
Total operating expenses	86,055	61,244	39,088
Loss from operations	(86,055)	(61,244)	(39,088)
Other income (expense):			
Interest income	2,644	1,547	169
Interest expense	(2,115)	(228)	(901)
Change in fair value of preferred stock tranche liability	—	—	4,443
Total other income (expense), net	529	1,319	3,711
Loss before income taxes	$ (85,526)	$ (59,925)	$ (35,377)
Income tax expense	24	—	—
Net loss	$ (85,550)	$ (59,925)	$ (35,377)
Other comprehensive loss			
Cumulative dividends on convertible preferred stock	—	—	(18,390)
Unrealized loss on marketable securities	(6)	—	—
Total other comprehensive loss	(6)	—	(18,390)
Net loss attributable to common stockholders	$ (85,556)	$ (59,925)	$ (53,767)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.04)	$ (5.00)	$ (56.10)
Weighted average common shares outstanding, basic and diluted	28,151,763	11,984,293	958,447
Pro forma net loss per share attributable to common stockholders, basic and diluted (unaudited)			$ (3.40)
Pro forma weighted average common shares outstanding, basic and diluted (unaudited)			11,689,795

(1) See Note 16 to our consolidated financial statements for further details on the calculation of net loss per share, basic and diluted, attributable to common stockholders and the weighted-average number of shares used in the computation of the per share amounts.

	As of December 31,	
	2019	2018
	(in thousands)	
Consolidated Balance Sheet Data:		
Cash, cash equivalents and marketable securities	$ 383,934	$ 114,592
Working capital (1)	364,234	102,643
Total assets	399,130	118,938
Long-term debt, net of discount, including current portion	29,642	—
Total stockholders' equity	337,584	104,158

(1) We define working capital as current assets less current liabilities.

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 related notes appearing elsewhere in this Annual Report on Form 10-K.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Overview

We are a clinical-stage biopharmaceutical company using our expertise in epigenetics to discover and develop novel therapeutics that address serious unmet medical needs in patients with cancers associated with abnormal gene expression or drug resistance. Our integrated epigenetics platform enables us to validate targets and generate small molecules impacting these targets to selectively modulate gene expression in tumor and immune cells to drive anti-tumor activity. This platform reflects our deep understanding of the biology of regulation of gene expression by epigenetic regulatory proteins, or epigenetic regulators, the development of small-molecule product candidates that selectively modulate their activity, and the design of clinical development programs supported by novel biomarker strategies. We are able to target a broad variety of epigenetic regulators using our platform and have generated development candidates acting against distinct classes of those regulators. Our vision is to become a late-stage oncology development company, with a broad pipeline of development and discovery programs.

To date, we have financed our operations primarily through our initial public offering, IPO, sales of our preferred and common stock, payments received in connection with collaboration and research agreements, borrowings under loan agreements, and sales from our Jefferies Sales Agreement.

As of December 31, 2019, we have funded our operations with the sales of convertible preferred stock, payments received in connection with collaboration agreements, borrowings under loan agreements and proceeds from our public and private offerings of our common stock.

On March 20, 2019, we entered into a Loan and Security Agreement, or the Loan Agreement, with Hercules Capital, Inc., or Hercules, pursuant to which we have borrowed $30.0 million and may borrow up to an additional $10.0 million subject to certain limitations. On October 3, 2019, we completed a private placement of an aggregate of 7,647,057 shares of our common stock and received net proceeds of approximately $64.9 million. In addition, on December 13, 2019, we completed a public offering of an aggregate of 7,475,000 of our common stock and received net proceeds of approximately $241.9 million.

Since our inception, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability, if ever, will depend heavily on the successful development and eventual commercialization of one or more of our product candidates. For the years ended December 31, 2019, 2018, and 2017, we reported a net loss of $85.6 million, $59.9 million and $35.4, respectively. As of December 31, 2019, we had an accumulated deficit of $319.4 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect that our expenses and capital requirements will increase substantially in connection with our ongoing activities, particularly if and as we:

- continue our MANIFEST trial, continue our ProSTAR trial, and continue our Phase 1/2 clinical trial of CPI-0209;
- advance our clinical-stage product candidates from mid-stage into later-stage trials, including our plans to conduct a Phase 3 trial of CPI-0610;
- continue the research and development of our other product candidates;
- seek to discover and develop additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval;

- scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;
- acquire or in-license products, product candidates or technologies;
- maintain, expand, enforce, defend and protect our intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and administrative personnel, including personnel to support our product development and planned future commercialization efforts and our operations as a public company.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. If we obtain regulatory approval for any of our product candidates, we expect to incur significant expenses related to developing our commercialization capability to support product sales, marketing and distribution. Further, we expect to incur additional costs associated with operating as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings; debt financings; collaborations; strategic alliances; and marketing, distribution or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, we may be unable to continue our operations at planned levels and may be forced to reduce or terminate our operations.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of $383.9 million. We believe that our cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2022. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. See “Liquidity and Capital Resources.”

Components of our Results of Operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the foreseeable future. If our development efforts for our product candidates are successful and result in regulatory approval, we may generate revenue in the future from product sales. We have entered into, and we may in the future enter into, license or collaboration agreements for our product candidates or intellectual property, and we may generate revenue in the future from payments as a result of such license or collaboration agreements. To date, all of our revenue has been derived from one collaboration arrangement. We cannot predict if, when, or to what extent we will generate revenue from the commercialization and sale of our product candidates. We may never succeed in obtaining regulatory approval for any of our product candidates.

Operating Expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses, including salaries, related benefits and stock-based compensation expense for employees engaged in research and development functions;
- expenses incurred in connection with the preclinical and clinical development of our product candidates and research programs, including under agreements with third parties, such as consultants and contractors and contract research organizations, or CROs;

- the cost of developing and scaling our manufacturing process and manufacturing drug products for use in our preclinical studies and clinical trials, including agreements with third parties, such as consultants and contractors and contract manufacturing organizations, or CMOs;
- laboratory supplies and research materials;
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities and insurance; and
- payments made under third-party licensing agreements.

In July 2012, we entered into a Research, Development and Commercialization Agreement, or the LLS Agreement, with the Leukemia & Lymphoma Society, or LLS, pursuant to which LLS committed to provide funding to us for research and development services, conditional on (i) the achievement of milestones in accordance with the LLS Agreement and (ii) equal funding being provided by us. We recognize the nonrefundable payments received under the LLS Agreement as a reduction to the research and development expenses incurred, based on a proportional methodology comparing the total expenses incurred in the period under the project to the total expenses expected to be incurred under the project. Through December 31, 2018, we had received funding totaling $7.3 million from LLS upon the achievement of specified milestones including $0.1 million received in 2018, which were recorded as a reduction of our research and development expenses. There was no additional funding received in the year ended December 31, 2019.

We expense research and development costs as incurred. Advance payments that we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs that include fees, reimbursed materials and other costs paid to consultants, contractors, CMOs and CROs in connection with our preclinical, clinical development and manufacturing activities. We do not allocate employee costs, costs associated with our discovery efforts, laboratory supplies and facilities expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple programs and our platform technology and, as such, are not separately classified.

Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will increase substantially in connection with our planned clinical and preclinical development activities in the near term and in the future as our current development programs progress and new programs are added. At this time, we cannot accurately estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our product candidates. The successful development and commercialization of our product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to raise additional funds necessary to complete clinical development of and commercialize our product candidates;
- the progress of the development efforts of parties with whom we may enter into collaboration arrangements;
- our ability to maintain our current research and development programs and to establish new ones;
- our ability to establish new licensing or collaboration arrangements;
- the successful initiation and completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority;
- the receipt and related terms of regulatory approvals from applicable regulatory authorities;
- the availability of raw materials for use in production of our product candidates;
- our ability to consistently manufacture our product candidates for use in clinical trials;

- our ability to establish and operate a manufacturing facility, or secure manufacturing supply through relationships with third parties;
- our ability to obtain and maintain intellectual property protection and regulatory exclusivity, both in the United States and internationally;
- our ability to maintain, enforce, defend and protect our rights in our intellectual property portfolio;
- the commercialization of our product candidates, if and when approved;
- our ability to obtain and maintain third-party coverage and adequate reimbursement;
- the acceptance of our product candidates, if approved, by patients, the medical community and third-party payors;
- competition with other products; and
- a continued acceptable safety profile of our therapies following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any of our product candidates.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in executive, finance and administrative functions. General and administrative expenses also include direct and allocated facility-related costs as well as professional fees for legal, patent, consulting, investor and public relations, accounting and audit services. We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs as well as investor and public relations expenses associated with operating as a public company.

Other Income (Expense)

Interest income

Interest income consists of interest earned on our invested cash balances and associated with our marketable securities. We expect our interest income to increase as we invest the cash received from the net proceeds from our offerings of common stock and net proceeds from borrowings under the Hercules Loan Agreement.

Interest expense

For the year ended December 31, 2019, interest expense consists of interest expense on borrowings under the Hercules Loan Agreement, as well as amortization of debt discount and debt issuance costs.

For the year ended December 31, 2018 and before, interest expense consists of interest expense on outstanding borrowings under our April 2016 loan and security agreement with Oxford Finance LLC and Silicon Valley Bank, or the 2016 Loan Agreement, as well as amortization of debt discount and debt issuance costs. Interest expense also consists of the change in the fair value of our preferred stock warrants. In connection with the 2016 Loan Agreement, we issued warrants to purchase Series B preferred stock. We classified these warrants as a liability on our balance sheet that we remeasured to fair value at each reporting date, and we recognized changes in the fair value of the warrant liability as interest expense in our statements of operations and comprehensive loss.

Upon the closing of our IPO, the preferred stock warrants became exercisable for common stock instead of preferred stock, and the fair value of the warrant liability at that time was reclassified to additional paid-in capital. As a result, we no longer remeasure the fair value of the warrant liability at each reporting date.

Income Taxes

Since our inception, we have not recorded any income tax benefits for the net losses we have incurred in each year or for our research and development tax credits, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our net operating loss carryforwards and tax credits will not be realized. As of December 31, 2019, we had U.S. federal and state net operating loss carryforwards of $317.4 million and $315.3 million, respectively, which may be available to offset future income tax liabilities and begin to expire in 2028. As of December 31, 2019, we also had U.S. federal and state research and development tax credit carryforwards of $12.1 million and $4.4 million, respectively, which begin to expire in 2028 and 2025, respectively. We have recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

On December 22, 2017, the Tax Cuts and Jobs Act, or the TCJA, was signed into U.S. law. The TCJA includes a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from 35% to 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely).

In connection with the TCJA, we remeasured certain deferred tax assets and liabilities based on the rates at which they are expected to reverse in the future, which is generally 21%. The remeasurement of our deferred tax balance was primarily offset by application of our valuation allowance. As of December 31, 2018, we had completed our accounting for all of the tax effects of the enactment of the TCJA; including the effects on our existing deferred tax balances. We had not recognized any material adjustment to the provisional estimate that was previously recorded related to the TCJA.

Results of Operations

Comparison of the Years Ended December 31, 2019 and 2018

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018:

	Year Ended December 31,		
	2019	2018	Change
	(in thousands)		
Operating expenses:			
Research and development	$ 66,459	$ 48,769	$ 17,690
General and administrative	19,596	12,475	7,121
Total operating expenses	86,055	61,244	24,811
Loss from operations	(86,055)	(61,244)	(24,811)
Other income (expense):			
Interest income	2,644	1,547	1,097
Interest expense	(2,115)	(228)	(1,887)
Total other income (expense), net	529	1,319	(790)
Loss before income taxes	(85,526)	(59,925)	(25,601)
Income tax expense	24	—	24
Net loss	$ (85,550)	$ (59,925)	$ (25,625)

Research and development expenses

	Year Ended December 31,		
	2019	2018	Change
	(in thousands)		
Direct research and development expenses by program:			
CPI-1205	$ 16,806	$ 14,919	$ 1,887
CPI-0610	15,462	4,835	10,627
CPI-0209	3,604	5,319	(1,715)
Preclinical pipeline	3,522	3,301	221
Unallocated expenses:			
Personnel related (including stock-based compensation)	18,425	13,210	5,215
Laboratory supplies and consumables	2,392	2,503	(111)
Facility related and other	6,248	4,682	1,566
Total research and development expenses	$ 66,459	$ 48,769	$ 17,690

Research and development expenses were $66.5 million for the year ended December 31, 2019 compared to $48.8 million for the year ended December 31, 2018. The increase in costs related to our CPI-1205 program was primarily due to increased enrollment in our ProSTAR trial, offset by the decreased cost of our ORIOn-E trial due to the orderly close out of such trial in 2019. The increase in costs related to our CPI-0610 program was primarily due to increased enrollment in our MANIFEST trial in 2019. The decrease in costs related to our CPI-0209 program was primarily due to the decrease in preclinical and process chemistry expenses as we moved into our Phase 1/2 clinical trial.

The increase in personnel related costs was primarily due to overall increase in headcount in our research and development function in 2019. Personnel related costs for year ended December 31, 2019 and 2018 included stock-based compensation expense of $2.7 million and $1.7 million, respectively. The increase in facility related and other costs was related to the additional office space rented and software licensed to support the increased headcount in 2019.

General and administrative expenses

	Year Ended December 31,		
	2019	2018	Change
		(in thousands)	
Personnel related (including stock-based compensation)	$ 11,232	$ 6,736	$ 4,496
Professional and consultant fees	4,265	2,942	1,323
Facility related and other	4,099	2,797	1,302
Total general and administrative expenses	$ 19,596	$ 12,475	$ 7,121

General and administrative expenses for the year ended December 31, 2019 were $19.6 million, compared to $12.5 million for the year ended December 31, 2018. The increase in personnel related costs was primarily due to increased headcount and increased stock-based compensation expense in 2019. Personnel related costs for the years ended December 31, 2019 and 2018 included stock-based compensation expense of $4.2 million and $2.3 million, respectively. Professional and consultant fees and facility related and other costs were increased due to consulting expenses associated with operating as a public company.

Other Income (Expense)

Interest income

Interest income increased to $2.6 million for the year ended December 31, 2019 from $1.5 million for year ended December 31, 2018 due to interest income associated with our marketable securities.

Interest expense

Interest expense was $2.1 million for the year ended December 31, 2019 and consisted primarily of cash and non-cash interest related to the Hercules Loan Agreement. Interest expense was $0.2 million for the years ended December 31, 2018 and consisted primarily of cash and non-cash interest related to the 2016 Loan Agreement, which was paid off in July 2018.

Comparison of the Years Ended

A discussion of changes in our results of operations during the year ended December 31, 2018 compared to the year ended December 31, 2017 has been omitted from this Annual Report on Form 10-K, but may be found in “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2018, filed with the SEC on March 14, 2019, which discussion is incorporated herein by reference and which is available free of charge on the SECs website at www.sec.gov.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. Through December 31, 2019, we have financed our operations primarily through sales of our preferred stock, payments received in connection with our collaboration and research agreements, borrowings under loan agreements, and proceeds from public and private offerings of our common stock. On March 20, 2019, we entered into the Loan Agreement with Hercules to provide up to $40.0 million in funding, to be made available in four tranches. As of December 31, 2019, we had drawn down on the first and second of the four tranches and in connection with the draw down received net proceeds of $29.5 million. On October 3, 2019, we completed a private placement of an aggregate of 7,647,057 shares of its common stock and received net proceeds of approximately $64.9 million. In addition, on December 13, 2019, we completed a public offering of an aggregate of 7,475,000 of its common stock and received net proceeds of approximately $241.9 million. As of December 31, 2019, we had cash, cash equivalents and marketable securities of $383.9 million.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	Year Ended December 31,		
	2019	2018	2017
	(in thousands)		
Cash used in operating activities	$ (72,248)	$ (48,823)	$ (37,586)
Cash used in investing activities	(49,609)	(476)	(582)
Cash provided by financing activities	341,597	147,670	17,652
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 219,740	$ 98,371	$ (20,516)

Operating activities

During the year ended December 31, 2019, operating activities used $72.2 million of cash, primarily resulting from our net loss of $85.6 million, partially offset by net non-cash expense of $7.5 million and net cash provided by changes in our operating assets and liabilities of $5.8 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2019 consisted primarily of a $5.9 million increase in accounts payable and accrued expenses and other current liabilities, $0.1 million net increase in operating lease, right-of-use assets and liabilities, partially offset by a $0.2 million increase in prepaid expenses and other current assets.

During the year ended December 31, 2018, operating activities used $48.8 million of cash, primarily resulting from our net loss of $59.9 million, partially offset by net non-cash expense of $4.7 million and net cash provided by changes in our operating assets and liabilities of $6.4 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2018 consisted primarily of a $7.9 million increase in accounts payable and accrued expenses and other current liabilities, partially offset by a $1.5 million increase in prepaid expenses and other current assets.

During the year ended December 31, 2017, operating activities used $37.6 million of cash, primarily resulting from our net loss of $35.4 million and net non-cash income of $2.5 million, partially offset by net cash provided by changes in our operating assets and liabilities of $0.3 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2017 consisted primarily of a $1.0 million increase in accounts payable and accrued expenses and other current liabilities, partially offset by a $0.8 million increase in prepaid expenses and other current assets.

Changes in accounts payable, accrued expenses and other current liabilities and prepaid expenses in all periods were generally due to growth in our business, the advancement of our research programs and the timing of vendor invoicing and payments.

Investing activities

During the year ended December 31, 2019, net cash used in investing activities was $49.6, primarily due to purchases of marketable securities totaling $114.7 million and purchases of property and equipment totaling $0.7 million, offset by proceeds from maturities and sales of marketable securities totaling $65.8 million. The purchases of property and equipment was related to equipment and software purchases to expand our discovery activities. During the years ended December 31, 2018 and 2017, net cash used in investing activities was $0.5 million, and $0.6 million, respectively, due to purchases of marketable securities in 2019 and purchases of property and equipment. The purchases of property and equipment during the year ended December 31, 2018 related to equipment and software purchases to expand our discovery activities. The purchases of property and equipment during the year ended December 31, 2017 related to purchases of new laboratory equipment.

Financing activities

During the year ended December 31, 2019, net cash provided by financing activities was $341.6 million, consisting primarily of net proceeds from our public offering of $241.9 million, net proceeds from our private placement of $64.9 million, net proceeds from borrowing under Loan Agreement of $29.5 million, net proceeds from exercise of stock option of $5.0 million, and net proceeds from sales from our Jefferies Sales Agreement of $0.1 million.

During the year ended December 31, 2018, net cash provided by financing activities was $147.7 million, consisting primarily of net proceeds from the issuance of Series F preferred stock of $99.6 million and net proceeds from our IPO of $52.2 million, partially offset by payments of $4.7 million on long-term debt and the final payment under the 2016 Loan Agreement.

During the year ended December 31, 2017, net cash provided by financing activities was $17.7 million, consisting primarily $24.2 million in proceeds from the issuance of convertible preferred stock, partially offset by payments of $6.6 million on long-term debt under the 2016 Loan Agreement.

Loan and Security Agreement

We previously had outstanding amounts due under an agreement of $11.8 million (the "2016 Loan Agreement"). Borrowings under the 2016 Loan Agreement bore interest at an annual rate of 7.6% and were repaid in full on July 3, 2018. In addition, a final payment equal to 5% of the original principal amount was paid upon the final principal payment.

On March 20, 2019, we entered into the Loan Agreement with Hercules as administrative and collateral agent, and various other lenders, pursuant to which we may borrow under a term loan up to an aggregate principal amount of $40.0 million, to be made available in four tranches. The outstanding principal balance as of December 31, 2019 is $30.0 million. As of December 31, 2019, we had drawn down on the first and second of the four tranches, and we have the ability to draw down the remainder of the tranches until March 31, 2020, subject to lender approval. The term loan bears interest at an annual rate equal to the greater of 8.55% and the prime rate of interest plus 2.55%. The Loan Agreement provides for interest-only payments until April 30, 2021, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on May 1, 2021 and continuing through April 1, 2023 (the "Maturity Date"). In addition, we paid a fee of $0.3 million upon closing and are required to pay a fee of 6.35% of the aggregate amount of advances under the Loan Agreement at maturity. At our option, we may elect to prepay all or a portion of the outstanding advances by paying the entire principal balance (or a portion thereof) and all accrued and unpaid interest thereon plus a prepayment charge equal to the following percentage of the principal amount being prepaid: 2% if an advance is prepaid during the first 12 months following the applicable advance date, 1% if an advance is prepaid after 12 months but prior to 24 months following the applicable advance date, and 0.5% if an advance is prepaid any time after 24 months following the applicable advance date but prior to the Maturity Date. In connection with the Loan Agreement, we granted Hercules a security interest in all of its personal property now owned or hereafter acquired, excluding intellectual property (but including the rights to payment and proceeds from the sale, licensing or disposition of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants. If we fail to make payments when due, or breaches any operational covenant or has any event of default, this could have a material adverse effect on our business and financial condition.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials for our product candidates in development. In addition, as a result of our IPO, we expect to continue to incur additional costs associated with operating as a public company. The timing and amount of our operating expenditures will depend largely on:

- the timing and progress of preclinical and clinical development activities;
- the commencement, enrollment or results of the planned clinical trials of our product candidates or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- the timing and outcome of regulatory review of our product candidates;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- our requirements and timing to expand headcount and facilities in order to support our growing operations:
- changes in laws or regulations applicable to our product candidates, including but not limited to clinical trial requirements for approvals;
- developments concerning our contract manufacturers;
- our ability to obtain materials to produce adequate product supply for any approved product or inability to do so at acceptable prices;
- our ability to establish additional collaborations if needed;

- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we obtain marketing approval;
- the legal patent costs involved in preparing, filing and prosecuting patent applications and maintaining, defending and enforcing patent claims and other intellectual property claims;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to the use of our product candidates; and
- the terms and timing of any collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of $383.9 million. We believe that our cash, cash equivalents and marketable securities, will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2022. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect.

Until such time as we can generate substantial product revenue, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or drug candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts, or grant rights to develop and market drug candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2019 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

	Payments Due By Period				
	Total	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More Than 5 Years
	(in thousands)				
Operating lease commitment (1)	$ 13,503	$ 3,592	$ 9,911	$ —	$ —
Debt obligations (2)	38,166	2,608	35,558	—	—
Total	$ 51,669	$ 6,200	$ 45,469	$ —	$ —

(1) Amounts in table reflects payments due for our lease of office and laboratory space in Cambridge, Massachusetts under an amendment of operating lease agreement that expires in June 2023.

(2) Amounts in table reflect the contractually required principal, interest and the final payment due under the Hercules Loan Agreement as of December 31, 2019.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. These contracts do not contain minimum purchase commitments and are cancelable by us upon prior written notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

The LLS Agreement requires us to make certain milestone payments to LLS, that could total up to $25.0 million in aggregate, upon our receipt of payments associated with the licensing or transfer of rights to the related compound (or a product) to a third party, upon first regulatory approval of a product in the U.S., or upon the first regulatory approval of a product in Europe or Japan. We have not included future payments under this agreement in the table of contractual obligations above since these obligations are contingent upon future events. As of December 31, 2019, we were unable to estimate the timing or likelihood of achieving these milestones.

We have also entered into license agreements with third parties, which are in the normal course of business. We have not included future payments under these agreements in the table of contractual obligations above since obligations under these agreements are contingent upon future events such as our achievement of specified development, regulatory and commercial milestones, or royalties on net product sales. As of December 31, 2019, we were unable to estimate the timing or likelihood of achieving these milestones or generating future product sales.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of financial condition and results of operations are based on our consolidated financial statements which are prepared in accordance with generally accepted accounting principles, or GAAP, in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that the estimates and assumptions involved in the accounting policies described below may have the greatest potential impact on our consolidated financial statements and, therefore, consider these to be our critical accounting policies. We evaluate our estimates and assumptions on an ongoing basis using historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Our actual results may differ from these estimates under different assumptions and conditions.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in the financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of the estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors in connection with preclinical development activities;
- CMOs in connection with the process development and scale up activities and the production of preclinical and clinical trial materials; and
- CROs and other providers in connection with clinical trials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs and CROs that supply materials and conduct services. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Stock-based Compensation

We measure stock-based awards granted to employees and directors based on their fair value on the date of the grant using the Black-Scholes option-pricing model. Compensation expense for those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. We use the straight-line method to record the expense of awards with service-based vesting conditions. We use the graded-vesting method to record the expense of awards with both service-based and performance-based vesting conditions, commencing when achievement of the performance condition becomes probable. We measure the fair value of stock-based awards granted to nonemployees on the date at which the related service is complete, which is generally the vesting date of the award. Prior to the service completion date, compensation expense is recognized over the period during which services are rendered by such nonemployees. At the end of each financial reporting period prior to the service completion date, the fair value of these awards is remeasured using the then-current fair value of our common stock and updated assumption inputs in the Black-Scholes option-pricing model.

The Black-Scholes option-pricing model uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our common stock options, the risk-free interest rate for a period that approximates the expected term of our common stock options, and our expected dividend yield.

Valuation of Warrants to Purchase Preferred Stock

We issued warrants to purchase preferred stock in 2013 and 2014 for the purchase of 375,000 shares of Series B Preferred Stock. Upon the closing of the IPO in July 2018, these warrants converted into warrants to purchase 34,062 shares of common stock at which time we reclassified the carrying value of the warrants to additional paid-in capital.

Prior to the warrants becoming warrants to purchase common stock, we were required to remeasure the fair value of the liability for these preferred stock warrants at each reporting date since their grant date, with any adjustments recorded in interest expense. The warrants outstanding at each reporting date were remeasured using the Black-Scholes option-pricing model, and the resulting change in fair value was recorded as interest expense in the statements of operations and comprehensive loss.

Valuation of Preferred Stock Tranche Liability

The Series E-1 preferred stock purchase agreement provided the Series E-1 investors with the right to participate in a subsequent closing of Series E-1 preferred stock upon the earlier of one year from the issuance date or the achievement of a strategic event as determined by the board of directors. The Series E-1 Tranche Right met the definition of a freestanding financial instrument as the Series E-1 Tranche Right was legally detachable and separately exercisable from the Series E-1 preferred stock. The Series E-1 Tranche Right was classified as a liability and initially recorded at fair value. The Series E-1 Tranche Right liability was subject to revaluation at each balance sheet date until its exercise in July 2017. We utilized the Black-Scholes option-pricing model, which incorporated assumptions and estimates to value the Series E-1 Tranche Right liability prior to its exercise. We assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Changes in fair value were included as a line item within other income (expense) in the accompanying statements of operations and comprehensive loss.

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.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our financial statements appearing elsewhere in this Annual Report on Form 10-K.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012 permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to “opt out” of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to “opt out” of such extended transition period or (ii) no longer qualify as an emerging growth company.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of $383.9 million. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio.

As of December 31, 2019, we had $30.0 million of borrowings outstanding under the Loan Agreement. This term loan bears interest at a variable annual rate equal to the greater of (i) 8.55% and (ii) the prime rate plus 2.55%, thereby exposing us to interest rate risk. Based upon the prime rate at December 31, 2019 of 4.75% and considering the $30.0 million of principal outstanding, an immediate 10% change in the Prime Rate would not have a material impact on our debt-related obligations, financial position or results of operation.

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with foreign vendors. Our operations may be subject to fluctuations in foreign currency exchange rates in the future.

Inflation would generally affect us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2019, and 2018.

Item 8. Financial Statements and Supplementary Data.

Index to Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Constellation Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Constellation Pharmaceuticals, Inc. (the Company) as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the “consolidated financial statements”). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with U.S. generally accepted accounting principles.

Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in year ended December 31, 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842).

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/ Ernst & Young LLP

We have served as the Company’s auditor since 2008.

Boston, Massachusetts

March 10, 2020

Constellation Pharmaceuticals, Inc.

Consolidated Balance Sheets

(In Thousands, Except Share and Per Share Amounts)

	December 31,	
	2019	**2018**
Assets		
Current assets:		
Cash and cash equivalents	$ 334,332	$ 114,592
Marketable securities	49,602	—
Prepaid expenses and other current assets	3,055	2,711
Total current assets	386,989	117,303
Property and equipment, net	971	1,210
Restricted cash	425	425
Operating lease, right-of-use assets	10,745	—
Total assets	$ 399,130	$ 118,938
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 7,278	$ 5,723
Accrued expenses and other current liabilities	12,915	8,937
Current portion of lease liabilities - operating lease	2,562	—
Total current liabilities	22,755	14,660
Long-term debt, net of current portion and discount	29,642	—
Operating lease liabilities, net of current portion	8,759	—
Deferred rent, net of current portion	—	118
Other long-term liabilities	390	2
Total liabilities	61,546	14,780
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized; no shares issued or outstanding at December 31, 2019 and 2018, respectively	—	—
Common stock, $0.0001 par value; 200,000,000 shares authorized at December 31, 2019 and 2018, respectively; 41,719,039 and 25,803,475 shares issued at December 31, 2019 and 2018, respectively; 41,719,039 and 25,803,135 shares outstanding at December 31, 2019 and 2018, respectively	4	3
Additional paid-in capital	656,973	337,992
Accumulated other comprehensive loss	(6)	—
Accumulated deficit	(319,387)	(233,837)
Total stockholders' equity	337,584	104,158
Total liabilities and stockholders' equity	$ 399,130	$ 118,938

The accompanying notes are an integral part of these consolidated financial statements.

Constellation Pharmaceuticals, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(In Thousands, Except Share and Per Share Amounts)

	Years Ended December 31,		
	2019	2018	2017
Operating expenses:			
Research and development	$ 66,459	$ 48,769	$ 32,617
General and administrative	19,596	12,475	6,471
Total operating expenses	86,055	61,244	39,088
Loss from operations	(86,055)	(61,244)	(39,088)
Other income (expense):			
Interest income	2,644	1,547	169
Interest expense	(2,115)	(228)	(901)
Change in fair value of preferred stock tranche liability	—	—	4,443
Total other income (expense), net	529	1,319	3,711
Loss before income taxes	(85,526)	(59,925)	(35,377)
Income tax expense	24	—	—
Net loss	$ (85,550)	$ (59,925)	$ (35,377)
Other comprehensive loss			
Cumulative dividends on convertible preferred stock	—	—	(18,390)
Unrealized loss on marketable securities	(6)	—	—
Total other comprehensive loss	(6)	—	(18,390)
Net loss attributable to common stockholders	$ (85,556)	$ (59,925)	$ (53,767)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.04)	$ (5.00)	$ (56.10)
Weighted average common shares outstanding, basic and diluted	28,151,763	11,984,293	958,447

The accompanying notes are an integral part of these consolidated financial statements.

Constellation Pharmaceuticals, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

(In Thousands, Except Share Amounts)

	Convertible Preferred Stock (Series A, B, D, E, E-1 and F)		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Gain	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balances at December 31, 2017	118,867,177	$ 173,228	962,898	$ —	$ 8,079	$ —	$ (173,912)	$ (165,833)
Issuance of Series F convertible preferred stock, net of issuance costs of $144	99,750,000	99,606	—	—	—	—	—	—
Conversion of convertible preferred stock into common stock upon closing of the initial public offering	(218,617,177)	(272,834)	20,501,927	2	272,832	—	—	272,834
Conversion of preferred stock warrants to common stock warrants upon closing of initial public offering	—	—	—	—	364	—	—	364
Issuance of common stock sold in initial public offering, net of underwriting discounts, commissions and offering costs	—	—	4,000,000	1	52,162	—	—	52,163
Repayment of promissory notes issued upon early exercise of unvested options	—	—	229,357	—	290	—	—	290
Stock-based compensation expense	—	—	—	—	3,952	—	—	3,952
Vesting of common stock issued upon early exercise of unvested options	—	—	664	—	4	—	—	4
Exercise of common stock warrant	—	—	51,032	—	79	—	—	79
Stock option exercises	—	—	57,257	—	230	—	—	230
Net loss	—	—	—	—	—	—	(59,925)	(59,925)
Balances at December 31, 2018	—	—	25,803,135	3	337,992	—	(233,837)	104,158
Issuance of common stock sold in equity offerings, net of underwriting discounts, commissions and offering costs	—	—	15,161,563	1	307,026	—	—	307,027
Stock-based compensation expense	—	—	—	—	6,910	—	—	6,910
Vesting of common stock issued upon early exercise of unvested options	—	—	340	—	—	—	—	—
Exercise of common stock warrant	—	—	7,919	—	—	—	—	—
Stock option exercises	—	—	746,082	—	5,045	—	—	5,045
Unrealized loss on marketable securities	—	—	—	—	—	(6)	—	(6)
Net loss	—	—	—	—	—	—	(85,550)	(85,550)
Balances at December 31, 2019	—	$ —	41,719,039	$ 4	$ 656,973	$ (6)	$ (319,387)	$ 337,584

The accompanying notes are an integral part of these consolidated financial statements.

Constellation Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In Thousands)

	Years Ended December 31,		
	2019	**2018**	**2017**
Cash flows from operating activities:			
Net loss	$ (85,550)	$ (59,925)	$ (35,377)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization expense	758	562	474
Stock-based compensation expense	6,910	3,952	1,151
Non-cash interest expense	507	45	326
Amortization and accretion on marketable securities	(698)	—	—
Change in fair value of preferred stock warrant liability	—	110	28
Change in fair value of preferred stock tranche liability	—	—	(4,443)
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(232)	(1,393)	(803)
Operating lease, right-of-use assets	3,308	—	—
Accounts payable	1,733	2,751	67
Accrued expenses and other current liabilities	4,177	5,184	915
Operating lease liabilities	(3,161)	—	—
Deferred rent	—	(127)	94
Other assets	—	18	(18)
Net cash used in operating activities	(72,248)	(48,823)	(37,586)
Cash flows from investing activities:			
Purchase of marketable securities	(114,685)	—	—
Purchases of property and equipment	(699)	(476)	(582)
Proceeds from maturities and sales of marketable securities	65,775	—	—
Net cash used in investing activities	(49,609)	(476)	(582)
Cash flows from financing activities:			
Proceeds from common stock offerings, net of underwriting discounts and commissions	307,027	55,801	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	99,606	24,231
Proceeds from issuance of long-term debt	29,650	—	—
Payment of debt issuance costs	(125)	—	—
Payments on long-term debt, including final payment	—	(4,698)	(6,634)
Proceeds from repayment of promissory notes issued upon early exercise of stock options	—	290	—
Payments of initial public offering costs	—	(3,638)	—
Proceeds from issuance of common stock upon stock option exercises	5,045	230	55
Proceeds from exercises of common stock warrants	—	79	—
Net cash provided by financing activities	341,597	147,670	17,652
Net increase (decrease) in cash, cash equivalents and restricted cash	219,740	98,371	(20,516)
Cash, cash equivalents and restricted cash at beginning of period	115,017	16,646	37,162
Cash, cash equivalents and restricted cash at end of period	$ 334,757	$ 115,017	$ 16,646
Supplemental disclosure of cash flow information:			
Interest paid	$ 1,387	$ 105	$ 546
Income taxes paid	$ 1	$ —	$ —
Supplemental disclosure of noncash investing and financing information:			
Purchases of property and equipment included in accounts payable	$ —	$ 180	$ 5
Vesting of common stock subject to repurchase	$ —	$ 4	$ 9

The accompanying notes are an integral part of these financial statements.

1. Nature of the Business and Basis of Presentation

Constellation Pharmaceuticals, Inc. ("Constellation" or the "Company") is a clinical-stage biopharmaceutical company using its expertise in epigenetics to discover and develop novel therapeutics that address serious unmet medical needs in patients with cancers associated with abnormal gene expression or drug resistance. The Company was incorporated in January 2008 as EpiGenetiX, Inc. under the laws of the State of Delaware. On March 31, 2008, the Company changed its name to Constellation Pharmaceuticals, Inc.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's drug development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The accompanying financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Since inception, the Company has funded its operations with the sales of convertible preferred stock, payments received in connection with collaboration agreements, borrowings under loan agreements, and proceeds from the initial public offering ("IPO") completed in July 2018. On March 20, 2019, the Company entered into a Loan and Security Agreement (the "Loan Agreement") with Hercules Capital, Inc. ("Hercules") pursuant to which Hercules agreed to provide the Company with up to $40.0 million in funding, to be made available in four tranches. December 31, 2019, the Company had drawn down on the first and second of the four tranches and in connection with the draw down received net proceeds of $29.5 million. On October 3, 2019, the Company completed a private placement of an aggregate of 7,647,057 shares of its common stock and received net proceeds of approximately $64.9 million. In addition, on December 13, 2019, the Company completed a public offering of an aggregate of 7,475,000 of its common stock and received net proceeds of approximately $241.9 million.

The Company has incurred recurring losses since inception, including net losses of $85.6 million, $59.9 million and $35.4 million for the year ended December 31, 2019, 2018, and 2017, respectively. As of December 31, 2019, the Company had an accumulated deficit of $319.4 million. The Company expects to continue to generate operating losses in the foreseeable future. As of March 10, 2020, the Company expects that its cash and cash equivalents will be sufficient to fund its operating expenses and capital expenditure requirements through at least 12 months from the issuance date of the financial statements.

The Company's financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP").

2. Summary of Significant Accounting Policies

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary, Constellation Securities Corporation, which was established on December 21, 2018. All significant intercompany balances and transactions have been eliminated in consolidation.

Use of estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these financial statements include, but are not limited to, revenue recognition, the accrual of research and development expenses, preferred stock tranche liability and stock-based awards. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates, as there are changes in circumstances, facts and experience. Actual results may differ from those estimates or assumptions.

Unaudited pro forma information

The accompanying unaudited pro forma balance sheet as of December 31, 2017 has been prepared to give effect to the automatic conversion of all shares of convertible preferred stock then outstanding into 10,731,348 shares of common stock and all warrants to purchase convertible preferred stock then outstanding becoming warrants to purchase common stock as if the proposed initial public offering had occurred on December 31, 2017.

In the accompanying statements of operations and comprehensive loss, the unaudited pro forma basic and diluted net loss per share attributable to common stockholders for the year ended December 31, 2017 has been prepared to give effect to the automatic conversion of all shares of convertible preferred stock outstanding into shares of common stock and all warrants to purchase convertible preferred stock becoming warrants to purchase common stock as if the proposed initial public offering had occurred on the later of January 1, 2017 or the issuance date of the convertible preferred stock or preferred stock warrant.

Concentrations of credit risk and of significant suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company maintains most of its cash and cash equivalents at two accredited financial institutions in amounts that could exceed federally insured limits. Cash equivalents are invested in an institutional money market fund. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Deferred offering costs

The Company capitalizes certain legal, accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of such equity financing, these costs are recorded in stockholders' equity (deficit) as a reduction of additional paid-in capital generated as a result of the offering. Should the in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the statements of operations and comprehensive loss.

Deferred financing costs

The Company capitalizes lender, legal and other third-party fees that are directly associated with obtaining access to capital under credit facilities. Debt issuance costs incurred in connection with obtaining access to capital are recorded in prepaid expenses and other current assets and are amortized over the availability period or term of the credit facility. Debt issuance costs related to a recognized debt liability are recorded as a direct reduction of the carrying amount of the debt liability.

Property and equipment

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation and amortization expense is recognized using the straight-line method over the estimated useful life of each asset as follows:

	Estimated Useful Life
Laboratory equipment	3 years
Computer equipment and software	3 years
Furniture and fixtures	3 years
Leasehold improvements	Shorter of useful life or remaining lease term

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in loss from operations. Expenditures for repairs and maintenance that do not improve or extend the lives of the respective assets are charged to expense as incurred, while costs of major additions and betterments are capitalized.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. An impairment loss would be recognized in loss from operations when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. The Company did not record any impairment losses on long-lived assets during the years ended December 31, 2019, 2018 or 2017.

Fair value measurements

Certain assets and liabilities are carried at fair value under GAAP. 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 on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The Company's cash equivalents and preferred stock warrant liability are carried at fair value, determined according to the fair value hierarchy described above (see Note 3). The carrying values of the Company's accounts payable and accrued expenses approximate their fair values due to the short-term nature of these liabilities. The carrying value of the Company's outstanding debt as of December 31, 2019 (see Note 8) approximated fair value (a Level 3 measurement) based on interest rates currently available to the Company.

Preferred stock tranche right

The Series E-1 preferred stock purchase agreement provided the investors with the right to participate in a subsequent closing of Series E-1 preferred stock upon the earlier of one year from the issuance date or the achievement of a strategic event as determined by the Company's board of directors (the "Series E-1 Tranche Right"). The Series E-1 Tranche Right met the definition of a freestanding financial instrument as the Series E-1 Tranche Right was legally detachable and separately exercisable from the Series E-1 preferred stock. The Series E-1 Tranche Right was classified as a liability and initially recorded at fair value. The preferred stock tranche liability was subject to revaluation at each balance sheet date until its exercise in 2017. Changes in fair value are included as a line item within other income (expense) in the accompanying statements of operations and comprehensive loss.

Segment information

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is the development of novel therapeutics in the field of epigenetics. All of the Company's tangible assets are held in the United States.

Revenue recognition

On January 1, 2018, the Company adopted the new revenue standard, discussed below under the heading "Recently Adopted Accounting Pronouncements", which amended revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries ("ASC 606"). Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, the Company performs the following five steps: (i)

identification of the contract(s) with the customer, (ii) identification of the promised goods or services in the contract and determination of whether the promised goods or services are performance obligations, (iii) measurement of the transaction price, (iv) allocation of the transaction price to the performance obligations, and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company only applies the five-step model to contracts when it is probable that it will collect consideration it is entitled to in exchange for the goods or services it transfers to the customer.

The Company accounts for a contract with a customer that is within the scope of ASC 606 when all of the following criteria are met: (i) the arrangement has been approved by the parties and the parties are committed to perform their respective obligations, (ii) each party's rights regarding the goods or services to be transferred can be identified, (iii) the payment terms for the goods or services to be transferred can be identified, (iv) the arrangement has commercial substance and (v) collection of substantially all of the consideration to which the Company will be entitled in exchange for the goods or services that will be transferred to the customer is probable.

The Company estimates the transaction price based on the amount of consideration the Company expects to be received for transferring the promised goods or services in the contract. The consideration may include both fixed consideration and variable consideration. At the inception of each arrangement that includes variable consideration, the Company evaluates the amount of the potential payments and the likelihood that the payments will be received. The Company utilizes either the most likely amount method or expected value method to estimate the transaction price based on which method better predicts the amount of consideration expected to be received. If it is probable that a significant revenue reversal would not occur, the variable consideration is included in the transaction price.

For arrangements that include development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such milestones and any related constraint, and if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue and net income (loss) in the period of adjustment.

For sales-based royalties, including milestone payments based on the level of sales, the Company determines whether the sole or predominant item to which the royalties relate is a license. When the license is the sole or predominant item to which the sales-based royalty relates, the Company recognizes revenue at the later of: (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

The Company allocates the transaction price based on the estimated standalone selling price. The Company must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the standalone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amounts the Company would expect to receive for each performance obligation.

For performance obligations which consist of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation in order to determine whether the combined performance obligation is satisfied over time or at a point in time. The Company determines the appropriate method of measuring progress of combined performance obligations satisfied over time for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company will recognize revenue from non-refundable, up-front fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license.

The Company receives payments from customers based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional.

Collaboration agreements

For collaboration agreements with a third party, to determine the appropriate statement of operations classification of the recognized funding, the Company first assesses whether the collaboration arrangement is within the scope of the accounting guidance for collaboration arrangements. If it is, the Company evaluates the collaborative arrangement for proper classification in the statement of operations based on the nature of the underlying activity and the Company assesses the payments to and from the collaborative partner. If the payments to and from the collaborative partner are not within the scope

of other authoritative accounting guidance, the Company bases the statement of operations classification for the payments received on a reasonable, rational analogy to authoritative accounting guidance, applied in a consistent manner. Conversely, if the collaboration arrangement is not within the scope of accounting guidance for collaboration arrangements, the Company assesses whether the collaboration arrangement represents a vendor/customer relationship. If the collaborative arrangement does not represent a vendor/customer relationship, the Company then classifies the funding payments received in the statement of operations and comprehensive loss as a reduction of the related expense that is incurred.

In July 2012, the Company entered into a Research, Development and Commercialization Agreement (the "LLS Agreement") with the Leukemia & Lymphoma Society ("LLS") pursuant to which LLS committed to provide financial support (the "Funding") to the Company for research and development services, conditional on (i) the achievement of milestones in accordance with the LLS Agreement and (ii) equal funding being provided by the Company. The Company concluded that the LLS Agreement was not within the scope of the accounting guidance for collaboration arrangements (see Note 15). Due to the co-funded nature of the payments and the Company's assessment that it did not have a vendor/customer relationship with LLS, the Company recognized the nonrefundable payments received under the agreement as a reduction to the research and development expenses incurred, based on a proportional methodology comparing the total expenses incurred in the period under the project to the total expenses expected to be incurred under the project.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries, stock-based compensation and benefits, facilities costs and laboratory supplies, depreciation, manufacturing expenses and external costs of outside vendors engaged to conduct preclinical development activities and clinical trials as well as the cost of licensing technology.

Upfront payments and milestone payments made for the licensing of technology are expensed as research and development in the period in which they are incurred. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Research contract costs and accruals

The Company has entered into various research and development contracts with companies both inside and outside of the United States. These agreements are generally cancelable, and related payments are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

Stock-based compensation

The Company measures stock-based awards granted to employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. Compensation expense for those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The straight-line method of expense recognition is applied to all awards with service-only conditions, while the graded vesting method is applied to all grants with both service and performance conditions. The Company records the expense for stock-based compensation awards subject to performance-based milestone vesting when management determines that achievement of the milestone is probable. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date.

For stock-based awards granted to nonemployees, compensation expense is recognized over the period during which services are rendered by such nonemployees until completed. At the end of each financial reporting period prior to completion of the services, the fair value of these awards is remeasured using the then-current fair value of the Company's common stock and updated assumption inputs in the Black-Scholes option-pricing model. The Company classifies stock-based compensation expense in its statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Marketable Securities

Marketable securities consist of investments with original maturities greater than ninety days. The Company classifies its investments with maturities beyond one year as short term based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio of marketable securities as available-for-sale. Accordingly, these marketable securities are recorded at fair value and unrealized gains and losses are reported as a component of accumulated other comprehensive loss in stockholders' equity. Realized gains and losses and declines in value judged to be other than temporary are included as a component of other income (expense), net based on the specific identification method. When determining whether a decline in value is other than temporary, the Company considers various factors, including whether the Company has the intent to sell the security, and whether it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis.

The Company evaluates its marketable securities with unrealized losses for other-than-temporary impairment. When assessing marketable securities for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary," the Company reduces the investment to fair value through a charge to the statement of operations and comprehensive loss. No such adjustments were necessary during the periods presented.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. There was no difference between net loss and comprehensive loss for each of the periods presented in the accompanying financial statements.

Cash, Cash Equivalents and Restricted Cash

Cash equivalents consists of highly liquid investments that are readily convertible into cash with original maturities of three months or less from the date of purchase. The Company has a policy of making investments only in government securities or with commercial institutions that have at least an investment grade credit rating. The Company invests its cash primarily in reverse repurchase agreements (RRAs), government securities and obligations, corporate debt securities and money market funds. RRAs are collateralized by deposits in the form of government securities and obligations for an amount not less than 102% of their value. The Company does not record an asset or liability as the Company is not permitted to sell or repledge the associated collateral. The Company has a policy that the collateral has at least the prevailing credit rating of US Government Treasuries and Agencies. The Company utilizes a third party custodian to manage the exchange of funds and ensure that collateral received is maintained at 102% of the value of the RRAs on a daily basis. RRAs have stated maturities of less than 30 days.

As of December 31, 2019, the Company classified $0.4 million as restricted cash related to a letter of credit issued as a security deposit in connection with Company's lease of its corporate office facilities (Note 13). Cash, cash equivalents and restricted cash consists of the following:

	December 31,	
	2019	2018
Cash and cash equivalents	$ 334,332	$ 114,592
Restricted cash	425	425
Cash, cash equivalents and restricted cash	$ 334,757	$ 115,017

Net income (loss) per share

The Company follows the two-class method when computing net income (loss) per share, as the Company has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net income (loss) attributable to common stockholders is computed by adjusting net income (loss) attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to common stockholders is computed by dividing the diluted net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of common stock equivalents.

The Company's convertible preferred stock contractually entitles the holders of such shares to participate in dividends but does not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive. The Company reported a net loss attributable to common stockholders for the years ended December 31, 2019, 2018 and 2017.

Income taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Recently adopted accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, "Leases (Topic 842)", which requires lessees to recognize leases on the balance sheet and disclose key information about leasing arrangements. The Company adopted ASU 2016-02 as of January 1, 2019, using the modified retrospective approach. Prior period amounts have not been adjusted. The main difference between previous GAAP ("Topic 840") and Topic 842 is the recognition of right-of-use lease assets and lease liabilities by lessees for those leases classified as operating leases under Topic 840. In addition, the Company elected the following practical expedients:

- the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allowed the Company to carry forward the historical lease classification;
- the short-term lease practical expedient, which allowed the Company to exclude short-term leases of less than 12 months from recognition in the unaudited consolidated balance sheets; and
- the bifurcation of lease and non-lease components practical expedient, which did not require the Company to bifurcate lease and non-lease components for all classes of assets.

The adoption of this accounting standard resulted in the recording of operating lease right-of-use ("ROU") assets and lease liabilities for lease arrangements with an initial term greater than twelve months of $3.1 million and $3.5 million, respectively, as of January 1, 2019. The difference between the operating lease assets and liabilities was recorded as an adjustment to "Other liabilities" on the consolidated and condensed balance sheets, primarily related to deferred rent (lease incentives). The adoption of ASU 2016-02 had no impact on Retained earnings. For additional information regarding how the Company is accounting for leases under Topic 842, refer to Note 12, *Leases*, in the "Notes to Condensed Consolidated Financial Statements" in this Form 10-K.

Recently issued accounting pronouncements

In June 2016, the FASB issued ASU 2016-13, "Financial Instruments – Credit Losses (Topic 326): *Measurement of Credit Losses on Financial Instruments*," which represents a new credit loss standard that will change the impairment model for most financial assets and certain other financial instruments. Specifically, this guidance will require entities to utilize a new "expected loss" model as it relates to trade and other receivables. In addition, entities will be required to recognize an allowance for estimated credit losses on available-for-sale debt securities, regardless of the length of time that a security has been in an unrealized loss position. The new guidance is effective for the Company for annual and interim periods beginning after December 15, 2022. Early adoption is permitted. The Company is currently evaluating the potential impact that the adoption of this guidance may have on the consolidated financial statements

In July 2017, the FASB issued ASU No. 2017-11, *Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480), Derivatives and Hedging (Topic 815) I. Accounting for Certain Financial Instruments with Down Round Features II. Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception* ("ASU 2017-11"). Part I applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred stock that contain down-round features. Part II replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. The new guidance is effective for the Company for annual periods beginning after December 15, 2019. Early adoption is permitted for all entities, including adoption in an interim period. The Company does not anticipate that the standard will have a significant impact on its financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Disclosure Framework – Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"), which modifies certain disclosure requirements on fair value measurements. The amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all periods presented upon their effective date. ASU 2018-13 is effective for fiscal years beginning after December 15, 2019 and interim periods within those years. The Company does not anticipate that the standard will have a significant impact on its financial statements.

In December 2019, the FASB issued ASU 2019-12, *Simplifying the Accounting for Income Taxes*, or ASU 2019-12, which includes amendments to simplify the accounting for income taxes by removing certain exceptions to the general principles in ASC 740, *Income Taxes*, or ASC 740. The amendments also improve consistent application of and simplify U.S. GAAP for other areas of ASC 740 by clarifying and amending existing guidance. The new guidance is effective for the Company for annual periods beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. Early adoption of the amendments is permitted. The Company is currently evaluating ASU 2019-12.

3. Fair Value Measurements

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values (in thousands):

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
Cash equivalents:				
Money market funds included in cash and cash equivalents	$ 303,345	$ —	$ —	$ 303,345
Commercial paper	—	8,986	—	8,986
Corporate debt securities	—	2,001	—	2,001
Reverse Repurchase Agreements (RRAs)	—	20,000	—	20,000
	$ 303,345	$ 30,987	$ —	$ 334,332
Marketable securities:				
Corporate debt securities	$ —	$ 12,748	$ —	$ 12,748
Commercial paper	—	26,808	—	26,808
Government securities	—	10,046	—	10,046
Total	$ —	$ 49,602	$ —	$ 49,602

	December 31, 2018			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds included in cash and cash equivalents	$ 114,592	$ —	$ —	$ 114,592
	$ 114,592	$ —	$ —	$ 114,592

Money market funds were valued by the Company using quoted prices in active markets for similar securities, which represent a Level 1 measurement within the fair value hierarchy. The fair value of Level 2 instruments classified as cash equivalents and marketable debt securities were determined through third-party pricing services.

During the years ended December 31, 2019 and 2018, there were no transfers between Level 1, Level 2 and Level 3.

4. Marketable Securities

The following table summarizes the Company's marketable securities and cash equivalents as of December 31, 2019. The Company did not hold any marketable securities as of December 31, 2018.

	December 31, 2019			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
(in thousands)				
Cash equivalents:				
Money market funds	$ 303,345	$ —	$ —	$ 303,345
Commercial paper	8,986	—	—	8,986
Corporate debt securities	2,001	—	—	2,001
Reverse Repurchase Agreements (RRAs)	20,000	—	—	20,000
Total cash equivalents	$ 334,332	$ —	$ —	$ 334,332
Marketable securities:				
Corporate debt securities	$ 12,753	$ —	$ (5)	$ 12,748
Commercial paper	26,808	—	—	26,808
Government securities	10,047	—	(1)	10,046
Total marketable securities	$ 49,608	$ —	$ (6)	$ 49,602
Total cash equivalents and marketable securities	$ 383,940	$ —	$ (6)	$ 383,934

5. Property and Equipment, net

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2019	2018
Laboratory equipment	$ 5,411	$ 5,603
Computer equipment and internal-use software	1,567	2,319
Furniture and fixtures	330	289
Leasehold improvements	466	240
	7,774	8,451
Less: Accumulated depreciation and amortization	(6,803)	(7,241)
	$ 971	$ 1,210

Depreciation and amortization expense were $0.8 million and $0.6 million for the years ended December 31, 2019 and 2018, respectively. During the year ended December 31, 2019 and 2018, the Company disposed of property and equipment with a gross book value and accumulated depreciation of $1.2 million and less than $0.1 million, respectively. There was no gain or loss resulting from the disposals.

6. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31,	
	2019	2018
Accrued employee compensation and benefits	$ 4,527	$ 2,726
Accrued external research and development expense	7,707	5,610
Accrued professional fees	184	255
Other	497	346
	$ 12,915	$ 8,937

7. Collaboration and Research Agreements

Leukemia & Lymphoma Society

The Company has a collaboration agreement (the "LLS Agreement") with the Leukemia and Lymphoma Society, ("LLS") pursuant to which LLS committed to provide funding to the Company for research and development services, conditional on (i) the achievement of milestones in accordance with the LLS Agreement and (ii) equal funding being provided by the Company. Through December 31, 2018, the Company received funding totaling $7.3 million from LLS upon the achievement of specified milestones, which were recorded as a reduction of research and development expense. There was no additional funding received in the year ended December 31, 2019.

The LLS Agreement requires the Company to make payments to LLS upon the Company's achievement of specified milestones that could total up to $25.0 million in aggregate (see Note 15).

8. Debt

The Company previously had outstanding amounts due under an agreement of $11.8 million (the "2016 Loan Agreement"). Borrowings under the 2016 Loan Agreement bore interest at an annual rate of 7.6% and were repaid in full on July 3, 2018. In addition, a final payment equal to 5% of the original principal amount was paid upon the final principal payment.

On March 20, 2019, the Company entered into the Loan Agreement with Hercules as administrative and collateral agent, and various other lenders, pursuant to which the Company may borrow under a term loan up to an aggregate principal amount of $40.0 million, to be made available in four tranches. The outstanding principal balance as of December 31, 2019 is $30.0 million. As of December 31, 2019, the Company had drawn down on the first and second of the four tranches, and it has the ability to draw down the remainder of the tranches until March 31, 2020, subject to lender approval. The term loan bears interest at an annual rate equal to the greater of 8.55% and the prime rate of interest plus 2.55%. The Loan Agreement provides for interest-only payments until April 30, 2021, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on May 1, 2021 and continuing through April 1, 2023 (the "Maturity Date"). In addition, the Company paid a fee of $0.3 million upon closing and is required to pay a fee of 6.35% of the aggregate amount of advances under the Loan Agreement at maturity. At its option, the Company may elect to prepay all or a portion of the outstanding advances by paying the entire principal balance (or a portion thereof) and all accrued and unpaid interest thereon plus a prepayment charge equal to the following percentage of the principal amount being prepaid: 2% if an advance is prepaid during the first 12 months following the applicable advance date, 1% if an advance is prepaid after 12 months but prior to 24 months following the applicable advance date, and 0.5% if an advance is prepaid any time after 24 months following the applicable advance date but prior to the Maturity Date. In connection with the Loan Agreement, the Company granted Hercules a security interest in all of its personal property now owned or hereafter acquired, excluding intellectual property (but including the rights to payment and proceeds from the sale, licensing or disposition of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants of the Company. If the Company fails to make payments when due, or breaches any operational covenant or has any event of default, this could have a material adverse effect on its business and financial condition.

As of December 31, 2019, notes payable consisted of the following:

	December 31, 2019
Principal amount of term loans	$ 30,000
Debt discount current portion	—
Less: Current portion	—
Long-term debt, net of current portion	30,000
Debt discount net of current portion	(358)
Long-term debt, net of discount and current portion	$ 29,642

9. Convertible Preferred Stock

As of April 5, 2018, the Company had issued Series A, Series B, Series D, Series E, Series E-1, and Series F convertible preferred stock (collectively the "Preferred Stock").

On July 23, 2018, upon the closing of the Company's IPO, all outstanding convertible preferred stock automatically converted into shares of common stock.

10. Warrants to Purchase Convertible Preferred Stock

The Company issued warrants to purchase convertible preferred stock in 2013 and 2014 for the purchase of 375,000 shares of Series B Preferred Stock. Upon the closing of the IPO in July 2018, these warrants became warrants to purchase 34,062 shares of common stock at which time the Company reclassified the carrying value of the warrants to additional paid-in capital.

Prior to the warrants becoming warrants to purchase common stock, the Company was required to remeasure the fair value of the liability for these preferred stock warrants at each reporting date since their grant date, with any adjustments recorded in interest expense. The warrants outstanding at each reporting date were remeasured using the Black-Scholes option-pricing model, and the resulting change in fair value was recorded in interest expense in the Company's statements of operations and comprehensive loss.

11. Equity

Preferred Stock

The Company has authorized preferred stock amounting to 5,000,000 shares as of December 31, 2019 and 2018, respectively. The authorized preferred stock was classified under stockholders' equity at December 31, 2019 and 2018.

Common Stock

As of December 31, 2019, the Company's certificate of incorporation, as amended and restated, authorized the Company to issue 200,000,000 shares of common stock, $0.0001 par value per share.

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are not entitled to receive dividends, unless declared by the Company's board of directors. No dividends have been declared or paid by the Company since its inception.

At-the-Market Offering

In August 2019, the Company entered into an Open Market Sale Agreement℠ (the "Jefferies Sales Agreement") with Jefferies LLC ("Jefferies"), under which Jefferies may offer and sell, from time to time, shares of common stock having aggregate gross proceeds of up to $50.0 million. At its option, the Company may sell shares of common stock through Jefferies as its sales agent, with any such sales being made by any method that is deemed an "at-the-market offering" as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (the "Securities Act"), or in other transactions pursuant to an effective shelf registration statement on Form S-3. The Company agreed to pay Jefferies a commission of up to 3% of the gross proceeds of any sales of common stock pursuant to the Jefferies Sales Agreement. In the third quarter of 2019, the Company began to issue and sell securities under the Jefferies Sales Agreement. During the year ended December 31, 2019, the Company sold 39,506 shares of common stock, for net cash proceeds of $0.1 million, after deducting commission fees and issuance costs of $0.2 million.

Private Placement

On October 3, 2019, the Company completed a private placement of an aggregate of 7,647,057 shares of its common stock and received net proceeds of approximately $64.9 million.

Follow On Offering

On December 13, 2019, the Company completed a public offering of an aggregate of 7,475,000 of its common stock and received net proceeds of approximately $241.9 million.

Warrants to Purchase Common Stock

As of December 31, 2017, the Company had outstanding warrants to purchase 112,900 shares of common stock with an exercise price of $1.55 per share. Upon the closing of the IPO in July 2018, the Company's preferred stock warrants became warrants to purchase 34,062 shares of common stock with an exercise price of $13.22 per share. In August 2018, 51,032 warrants with an exercise price of $1.55 per share were exercised. As of December 31, 2019, the Company has outstanding warrants to purchase common stock as follows:

Issuance Date	Term (in years)	Exercise Price	Number of Common Shares Issuable under Warrant
May 23, 2011	10	$ 1.55	61,868
September 30, 2014	10	$ 13.22	22,708
			84,576

12. Stock-based Compensation

2008 Stock Incentive Plan

The Company's 2008 Stock Incentive Plan (the "2008 Plan") provided for the Company to grant incentive stock options or nonqualified stock options, restricted stock, restricted stock units and other equity awards to employees, directors, consultants and advisors of the Company. The 2008 Plan was administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The board of directors could also delegate to one or more officers of the Company the power to grant awards to employees and certain officers of the Company. The exercise prices, vesting and other restrictions were determined at the discretion of the board of directors, or its committee if so delegated. Stock options granted under the 2008 Plan with service-based vesting conditions generally vest over four years and expire after ten years.

The total number of shares of common stock that were authorized for issuance under the 2008 Plan was 4,039,829 shares. Upon effectiveness of the Company's 2018 Equity Incentive Plan, the ("2018 Plan") in July 2018, the remaining 245,557 shares available under the 2008 Plan became available for issuance under the 2018 Plan and no future issuance will be made under the 2008 Plan. Additionally, outstanding options under the 2008 Plan that expired, terminated, are surrendered or canceled without having been fully exercised will be available for future awards under the 2018 Plan.

The exercise price for stock options granted is not less than the fair value of common shares as determined by the board of directors as of the date of grant. The Company's board of directors valued the Company's common stock, taking into consideration its most recently available valuation of common stock performed by third parties as well as additional factors which may have changed since the date of the most recent contemporaneous valuation through the date of grant.

2018 Equity Incentive Plan

In June 2018, the Company's stockholders approved the 2018 Plan, which became effective on July 18, 2018. The 2018 Plan provides for the grant of incentive stock options, non-qualified options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The number of shares initially reserved for issuance under the 2018 Plan is 2,779,544 plus the 245,557 shares of common stock remaining available for issuance under the 2008 Plan as of that date. The number of shares reserved shall be annually increased on each January 1 through January 1, 2028 by the least of (i) 2,216,368 shares, (ii) 4% of the number of shares of the Company's common stock outstanding on the first day of the year or (iii) an amount determined by the Company's board of directors. The shares of common stock underlying any awards that are expired, forfeited, canceled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, repurchased or are otherwise terminated by the Company under the 2018 Plan or the 2008 Plan will be added back to the shares of common stock available for issuance under the 2018 Plan. As of December 31, 2019, 1,677,943 shares remained available for future issuance under the 2018 Plan. In January 2020, the shares under the 2018 Plan were increased by 1,668,762 shares pursuant to the annual increase described above.

2018 Employee Stock Purchase Plan

In June 2018, the Company's stockholders approved the 2018 Employee Stock Purchase Plan which became effective on July 18, 2018. A total of 272,504 shares of common stock were reserved for issuance under this plan. The number of shares reserved shall be annually increased on each January 1 thereafter through January 1, 2028 by the least of (i) 545,008 shares, (ii) 1% of the number of shares of the Company's common stock outstanding on the first day of the year or (iii) an amount determined by the Company's board of directors. In January 2020, the shares under the 2018 Employee Stock Purchase Plan were increased by 417,190 shares pursuant to the annual increase described above.

Stock option valuation

The fair value of stock option grants is estimated using the Black-Scholes option-pricing model. The Company historically has been a private company and lacks company-specific historical and implied volatility information. Therefore, it estimates its expected stock volatility based on the historical volatility of a representative group of public companies in the biotechnology industry and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. For options with service-based vesting conditions, the expected term of the Company's stock options has been determined utilizing the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, for awards that qualify as "plain-vanilla" options. The expected term of stock options granted to nonemployees is equal to the contractual term of the option award. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of stock options granted to employees and directors:

	Year Ended December 31,		
	2019	2018	2017
Risk-free interest rate	2.30%	2.79%	2.04%
Expected volatility	82.21%	81.06%	79.82%
Expected dividend yield	—	—	—
Expected term (in years)	6.03	6.05	6.00

The following table summarizes the Company's option activity since December 31, 2018:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2018	3,779,403	$ 7.78	8.80	110.00
Granted	1,515,399	10.79		
Exercised	(746,422)	6.76		
Forfeited	(337,312)	8.86		
Outstanding as of December 31, 2019	4,211,068	$ 8.95	8.39	$ 160,689
Vested and expected to vest as of December 31, 2019	4,211,068	$ 8.95	8.39	$ 160,689
Options exercisable as of December 31, 2019	1,256,048	$ 7.39	7.71	$ 49,882

Prior to July 2016, the Company's stock option agreements allowed for the exercise of unvested stock option awards. The unvested shares are subject to repurchase by the Company if the employees cease to provide service to the Company, with or without cause. The table above reflects unvested stock options as exercised on the dates that the shares are no longer subject to repurchase. Payment for unvested shares is recorded as a long-term liability in the accompanying balance sheets. The liability for unvested common stock subject to repurchase is then reclassified into stockholders' equity as the shares vest. As of December 31, 2019 and 2018, options for the purchase of zero and 340 shares of common stock, respectively, had been exercised but were unvested and subject to repurchase. As December 31, 2019 and 2018, the long-term liability related to the payments for unvested shares was none and less than $0.1 million, respectively. For options granted after July 2016, the Company's stock option agreements no longer allow for early exercise of the options.

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had strike prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2019 and 2018 was $17.7 million and $0.2 million, respectively.

The weighted average grant-date fair value of awards granted during each of the years ended December 31, 2019 and 2018 were $7.63 and $6.66 per share, respectively.

As of December 31, 2019, there were outstanding unvested service-based stock options held by nonemployees for the purchase of 25,195 shares of common stock.

Stock-based compensation

The Company recorded stock-based compensation expense in the following expense categories of its statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Research and development expenses	$ 2,703	$ 1,668	$ 559
General and administrative expenses	4,207	2,284	592
Total	$ 6,910	$ 3,952	$ 1,151

As of December 31, 2019, total unrecognized compensation cost related to the unvested stock-based awards was $18.5 million, which is expected to be recognized over a weighted average period of 2.71 years.

13. Leases

The Company has leases for office and laboratory space. The Company occupies approximately 36,309 square feet of office and laboratory space in Cambridge, Massachusetts under a lease that originally expired in June 2020 and an additional 11,237 of office space in the same facility which originally expired in February 2022. In June 2019, the Company executed an amendment to extend the term of the lease until June 30, 2023. The Company determined that these leases are operating leases.

In June 2019, the Company entered into a sublease agreement for a portion of its office space consisting of approximately 4,422 square feet. The sub-lease commenced on June 21, 2019, (the "2019 sublease") and expires on June 20, 2020.

The Company recognizes its minimum rental expense on a straight-line basis over the term of the lease beginning with the date of initial control of the asset. With the adoption of ASC 842 the Company recognized all leases with terms greater than 12 months in duration on its Consolidated Balance Sheets as right-of-use assets and lease liabilities as of January 1, 2019. The Company adopted the standard using the modified retrospective approach.

Upon adoption of ASC 842 on January 1, 2019, the Company recorded operating lease assets of $3.1 million and operating lease liabilities of $3.5 million. The adoption of ASC 842 did not have a material impact on its consolidated statements of operations. Prior periods are presented in accordance with ASC 840, *Leases*.

The Company has made certain assumptions and judgments when applying ASC 842, the most significant of which are:

- The Company elected the package of practical expedients available for transition which allow it to not (i) reassess whether expired or existing contracts contain leases under the new definition of a lease, (ii) determine lease classification for expired or existing leases and (iii) determine whether previously capitalized initial direct costs would qualify for capitalization under ASC 842.
- The Company did not elect to use hindsight when considering judgments and estimates such as assessments of lessee options to extend or terminate a lease or purchase the underlying asset.
- For all asset classes, the Company elected to not recognize a right-of-use asset and lease liability for short-term leases of less than 12 months.
- For all asset classes, the Company elected to not separate non-lease components from lease components to which they relate and have accounted for the combined lease and non-lease components as a single lease component.
- The Company use its incremental borrowing rate to calculate the present value of its lease payments, as the implicit rates in its leases are not readily determinable.

As of December 31, 2019, assets under operating lease were $10.7 million. The elements of lease expense were as follows (in thousands)

	For the Year Ended December 31, 2019
Lease cost:	
Operating lease cost	$ 3,735
Sublease income	(199)
Total Lease cost	$ 3,536
Other information:	
Operating cash flows used for operating leases	$ 3,161
Operating lease liabilities arising from obtaining right-of-use assets	$ 11,321
Weighted-average remaining lease term in years	3.5
Weighted-average discount rate	10.37%

Future minimum lease payments under the operating lease as of December 31, 2019 are as follows (in thousands):

Year Ending December 31,	
2020	$ 3,592
2021	3,881
2022	3,997
2023	2,033
	$ 13,503
Present value adjustment	(2,182)
Present value of lease liabilities	$ 11,321

The Company adopted ASC 842, *Leases* on January 1, 2019, as noted above and, as required, the following disclosure is provided for periods prior to adoption. Future minimum lease payments required under non-cancelable operating leases in effect as of December 31, 2018 were as follows (in thousands):

Year Ending December 31,	
2019	$ 3,174
2020	2,122
2021	896
2022	150
	$ 6,342

Rent expense under operating leases was $ 2.3 million for the year ended December 31, 2018, which was prior to the adoption of ASC 842, *Leases.*

14. Income Taxes

2017 U.S. tax reform

On December 22, 2017, the Tax Cuts and Jobs Act (the “TCJA”) was signed into U.S. law. The TCJA includes a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from 35% to 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely).

In connection with the TCJA, the Company remeasured certain deferred tax assets and liabilities based on the rates at which they are expected to reverse in the future, which is generally 21%. The remeasurement of the Company' deferred tax balance was primarily offset by application of its valuation allowance. As of December 31, 2018, the Company had completed its accounting for all of the tax effects of the enactment of the TCJA; including the effects on its existing deferred tax balances. The Company had not recognized any material adjustment to the provisional estimate that was previously recorded related to the TCJA.

Income taxes

During the years ended December 31, 2019, 2018, and 2017, the Company recorded $24.0 thousand and no income tax, respectively for the net operating losses incurred or for the research and development tax credits generated in each year due to its uncertainty of realizing a benefit from those items. The $24 thousand recorded in 2019 represents state income taxes.

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,		
	2019	2018	2017
Federal statutory income tax rate	21.0 %	21.0 %	34.0 %
State taxes, net of federal benefit	7.4	6.2	5.7
Federal and state research and development tax credit	4.7	4.1	5.6
Warrant Settlement	—	—	4.3
Permanent items	3.3	(0.3)	(2.6)
Impact of the Tax Cuts and Jobs Act	—	—	(56.9)
Other	—	(0.1)	(0.2)
Change in deferred tax asset valuation allowance	(36.4)	(30.9)	10.1
Effective income tax rate	0.0 %	0.0 %	0.0 %

Net deferred tax assets consisted of the following (in thousands):

	December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 86,575	$ 61,147
Research and development tax credit carryforwards	15,611	11,574
Depreciation and amortization	73	39
Other	6,154	1,593
Total deferred tax assets	108,413	74,353
Valuation allowance	(105,478)	(74,353)
Deferred tax liabilities:	$ 2,935	$ —
Right of use assets	(2,935)	—
Total deferred tax liabilities	$ (2,935)	$ —

As of December 31, 2019, the Company had U.S. federal and state net operating loss carryforwards of $317.4 million and $315.3 million, respectively, which may be available to offset future income tax liabilities. Federal net operating loss carryforwards of $168.9 million will expire at various dates from 2028 to 2037. $148.5 million of the federal net operating loss can be carried forward indefinitely. State net operating loss carryforwards of $315.3 million will expire at various dates from 2030 to 2039. As of December 31, 2019, the Company also had U.S. federal and state research and development tax credit carryforwards of $12.1 million and $4.4 million, respectively, which may be available to offset future income tax liabilities and begin to expire in 2028 and 2025, respectively.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986, and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company completed several financings through December 31, 2011, which resulted in ownership changes in excess of 50%. The Company prepared an analysis to determine the effect of the ownership change limitation on its ability to utilize its net

operating loss and tax credit carryforwards, and concluded that as a result of ownership changes that occurred during 2008, there are restrictive limitations on approximately $1.9 million of the Company's net operating loss carryforwards and approximately $0.1 million of the Company's tax credit carryforwards. These limitations are reflected in the Company's net operating loss carryforwards and tax credit carryforwards presented herein. Subsequent ownership changes may further affect the limitation in future years. The Company has not conducted a study to assess whether a change of control has occurred since 2011 due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since 2011, utilization of the net operating loss carryforwards or research and development tax credit carryforwards generated since 2011 would be subject to an annual limitation under Section 382, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitation may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before utilization. Further, until an additional study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products or generation of any revenue from product sales since inception and has concluded that it is more likely than not that the Company will not realize all of the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been established against the deferred tax assets as of December 31, 2019 and 2018. Management reevaluates the positive and negative evidence at each reporting period.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2019 and 2018 related primarily to the increase in net operating loss carryforwards and research and development tax credit carryforwards in 2019 and 2018, and were as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Valuation allowance as of beginning of year	$ 74,353	$ 55,813
Increases recorded to income tax provision	31,125	18,540
Valuation allowance as of end of year	$ 105,478	$ 74,353

As of December 31, 2019 and 2018, the Company had not recorded any amounts for unrecognized tax benefits. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision. As of December 31, 2019 and 2018, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts had been recognized in the Company's statements of operations and comprehensive loss. The Company files income tax returns in the United States and Massachusetts. The federal and state income tax returns are generally subject to tax examinations for the tax years ended December 31, 2016 through December 31, 2019. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state taxing authorities to the extent utilized in a future period. No federal or state tax audits are currently in process.

15. Commitments and Contingencies

Research Agreements

The LLS Agreement requires the Company to make certain milestone payments to LLS, that could total up to $25.0 million in the aggregate, upon the receipt of payments by the Company associated with the licensing or transfer of rights to the related compound (or a product) to a third party, upon first regulatory approval of a product in the U.S., or upon the first regulatory approval of a product in Europe or Japan. As of December 31, 2019, and 2018, no events have occurred that would require payment of the milestones.

The Company has several in-license agreements with academic organizations. The Company is obligated to pay annual license maintenance fees of less than $0.1 million per year as well as reimburse certain institutions for costs incurred related to the filing, prosecution and maintenance of patent rights licensed under the agreements. In addition, the Company may be obligated to pay contingent milestone payments of up to a maximum of $15.7 million upon the achievement of certain defined events as well as royalties of low single-digit percentages of sales of licensed products. In certain cases, the maximum payments to the academic organizations are capped. If the Company grants any sublicense rights under the license agreements, the Company has agreed to pay a percentage of sublicense fees received by the Company to the licensors. As of December 31, 2019, and 2018, no events have occurred that would require payment of the milestones, royalties, or sublicense fees.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company does not believe that the outcome of any claims under indemnification arrangements will have a material effect on its financial position, results of operations or cash flows, and it has not accrued any liabilities related to such obligations in its financial statements as of December 31, 2019, and 2018.

Legal Proceedings

At each reporting date, we evaluate whether or not a potential loss amount or a potential range of losses is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. We expense as incurred the costs related to such legal proceedings. On January 17, 2017, a participant dosed in one of the Company's clinical trials filed a complaint against us in the United States District Court for the District of Arizona, alleging negligence, lack of informed consent, strict products liability and loss of consortium. The parties have reached agreement with regards to a resolution.

16. Net Loss and Unaudited Pro Forma Net Loss Per Share

Net loss per share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2019	2018
Numerator:		
Net loss	$ (85,550)	$ (59,925)
Unrealized loss on marketable securities	(6)	—
Net loss attributable to common stockholders	$ (85,556)	$ (59,925)
Denominator:		
Weighted average common shares outstanding, basic and diluted	28,151,763	11,984,293
Net loss per share attributable to common stockholders, basic and diluted	$ (3.04)	$ (5.00)

The Company's potential dilutive securities, which include warrants for the purchase of common stock and common stock options, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	December 31,	
	2019	2018
Warrants for the purchase of common stock	84,576	95,930
Options to purchase common stock	4,211,068	3,779,403
	4,295,644	3,875,333

17. Retirement Plan

The Company has a defined-contribution plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. As currently established, the Company is not required to make contributions to the 401(k) Plan. The Company made matching contributions of $0.4 million and $0.3 million for the years ended December 31, 2019 and 2018, respectively.

18. Selected Quarterly Financial Data (unaudited)

The following table contains selected consolidated quarterly financial information from 2019 and 2018. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	Three months ended			
	March 31, 2019	June 30, 2019	September 30, 2019	December 31, 2019
	(In thousands, except per share data)			
Total operating expenses	$ 20,106	$ 20,841	$ 21,051	$ 24,057
Total other income (expense), net	680	74	(98)	(127)
Net loss and comprehensive loss	$ (19,426)	$ (20,767)	$ (21,149)	$ (24,208)
Net loss attributable to common stockholders	$ (19,417)	$ (20,765)	$ (21,159)	$ (24,215)
Net loss per share attributable to common stockholders, basic and diluted	$ (0.75)	$ (0.80)	$ (0.82)	$ (0.69)

	Three months ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(In thousands, except per share data)			
Total operating expenses	$ 12,177	$ 12,022	$ 16,413	$ 20,632
Total other income (expense), net	75	81	475	688
Net loss and comprehensive loss	$ (12,102)	$ (11,941)	$ (15,938)	$ (19,944)
Net loss attributable to common stockholders	$ (12,102)	$ (11,941)	$ (15,938)	$ (19,944)
Net loss per share attributable to common stockholders, basic and diluted (1)	$ (12.44)	$ (9.96)	$ (0.81)	$ (0.77)

(1) The explanation for major variances of net loss per share from the first and second quarters for the year ended December 31, 2018 are: On July 23, 2018, upon the closing of the Company's IPO, all outstanding convertible preferred stock automatically converted into shares of common stock.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based upon that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2019 at the reasonable assurance level.

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 defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. Our management, under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer, conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2019 based on the framework in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework). Based on the results of its evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2019.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2019 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Except to the extent provided below, the information required by this Item 10 will be included in the section captioned “Corporate Governance Matters” and the subsections thereof, “Nominees for Election as Class II Directors,” “Class I Directors,” “Class III Directors,” “Information about our Executive Officers,” and “Delinquent Section 16(a) Reports,” in our definitive proxy statement to be filed with the Securities and Exchange Commission (“SEC”) with respect to our 2020 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

We post our code of business conduct and ethics, which applies to all employees, including all executive officers, senior financial officers and directors, in the “Corporate Governance” sub-section of the “Investor Relations” section (ir.constellationpharma.com) of our corporate website at www.constellationpharma.com. Our code of business conduct and ethics complies with Item 406 of SEC Regulation S-K and the rules of Nasdaq. We intend to disclose any changes to the code that affect the provisions required by Item 406 of Regulation S-K, and any waivers of the code of ethics for our executive officers, senior financial officers or directors, on our corporate website.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in the section captioned “Executive Compensation” in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

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

The information required by this Item 12 will be included in the sections captioned “Security Ownership of Certain Beneficial Owners and Management” and “Securities Authorized for Issuance under Equity Compensation Plans” in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

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

The information required by this Item 13 will be included in the sections captioned “Related Person Transactions,” “Policies and Procedures for Related Person Transactions” and “Board Determination of Independence” in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be included in the section captioned “Audit Fees and Services” and the subsection thereof in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) Consolidated Financial Statements

See Index to Consolidated Financial Statements at Item 8 herein.

(2) Financial Statement Schedules

All schedules are omitted because they are not applicable or the required information is shown in the consolidated financial statements or notes thereto.

(3) Exhibits

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
3.1	Amended and Restated Certificate of Incorporation of the Registrant	8-K	001-38584	7/23/2018	3.1	
3.2	Amended and Restated Bylaws of the Registrant	8-K	001-38584	7/23/2018	3.2	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1	333-225822	6/22/2018	4.1	
4.2	Description of Securities					*
10.1	Fifth Amended and Restated Investor Rights Agreement, dated as of March 22, 2018, by and among the Registrant and the other parties thereto	S-1	333-225822	6/22/2018	10.1	
10.2+	Amended and Restated 2008 Stock Incentive Plan (incorporated by reference to Exhibit 10.2 of the Registrant's Registration Statement on Form S-1, filed with the SEC on June 22, 2018)	S-1	333-225822	6/22/2018	10.2	
10.3+	Form of Incentive Stock Option Agreement under the 2008 Stock Incentive Plan	S-1	333-225822	6/22/2018	10.3	
10.4+	Form of Nonstatutory Stock Option Agreement under the 2008 Stock Incentive Plan	S-1	333-225822	6/22/2018	10.4	
10.5+	2018 Equity Incentive Plan	S-1	333-225822	6/22/2018	10.5	
10.6+	Form of Stock Option Agreement under the 2018 Equity Incentive Plan	S-1	333-225822	6/22/2018	10.6	
10.7+	2018 Employee Stock Purchase Plan	S-1	333-225822	6/22/2018	10.7	
10.8+	Summary of Non-Employee Director Compensation Program	S-1	333-225822	6/22/2018	10.8	
10.9†	Research, Development and Commercialization Agreement, dated as of July 31, 2012, by and between the Registrant and The Leukemia & Lymphoma Society, as amended	S-1	333-225822	6/22/2018	10.10	
10.10	Warrant to purchase shares of Series B preferred stock issued on June 28, 2013 by the Registrant to Oxford Finance LLC	S-1	333-225822	6/22/2018	10.12	
10.11	Warrant to purchase shares of Series B preferred stock issued on June 28, 2013 by the Registrant to Silicon Valley Bank	S-1	333-225822	6/22/2018	10.13	
10.12	Warrant to purchase shares of Series B preferred stock issued on September 30, 2014 by the Registrant to Oxford Finance LLC	S-1	333-225822	6/22/2018	10.14	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.13	Warrant to purchase shares of Series B preferred stock issued on September 30, 2014 by the Registrant to Oxford Finance LLC	S-1	333-225822	6/22/2018	10.15	
10.14	Form of Common Stock Purchase Warrant, dated May 24, 2011	S-1	333-225822	6/22/2018	10.16	
10.15	Lease Agreement, dated as of February 5, 2010, by and between the Registrant and ARE-MA Region No. 38 LLC, as amended	S-1	333-225822	6/22/2018	10.17	
10.16+	Letter Agreement, dated March 13, 2017, by and between the Registrant and Jigar Raythatha	S-1	333-225822	6/22/2018	10.18	
10.17+	Letter Agreement, dated August 30, 2017, by and between the Registrant and Emma Reeve	S-1	333-225822	6/22/2018	10.19	
10.18+†	Amended and Restated Letter Agreement, dated June 28, 2018, by and between the Registrant and Adrian Senderowicz	10-Q	001-38584	8/14/2018	10.5	
10.19+	Amended and Restated Change in Control Severance Plan	S-1	333-225822	6/22/2018	10.21	
10.20+	Consulting Agreement, dated as of May 2, 2017, by and between the Registrant and Oncology Drug Development, LLC	S-1	333-225822	6/22/2018	10.22	
10.21+	Consulting Agreement, dated as of July 15, 2017, by and between the Registrant and Dr. James Audia	S-1	333-225822	6/22/2018	10.23	
10.22+	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-225822	6/22/2018	10.24	
10.23	Loan and Security Agreement, dated as of March 20, 2019, by and among the Registrant, the several banks and other financial institutions or entities from time to time parties thereto and Hercules Capital, Inc.	8-K	001-38584	3/21/2019	10.1	
10.24	Fifth Amendment to Lease, dated as of June 17, 2019, between the Registrant and ARE-MA Region No. 38, LLC	10-Q	001-38584	8/07/2019	10.1	
10.25	Securities Purchase Agreement, dated October 1, 2019, by and among the Company and the other parties thereto.	8-K	001-38584	10/1/2019	10.1	
10.26	Registration Rights Agreement, dated October 1, 2019, by and among the Company and the other parties thereto.	8-K	001-38584	10/1/2019	10.2	
21.1	Subsidiaries of the Registrant					*
23.1	Consent of Ernst & Young LLP, independent registered public accounting firm					*
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					*
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					*
32.1	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					*

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
32.2	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					*
101.INS	XBRL Instance Document					
101.SCH	XBRL Taxonomy Extension Schema Document					
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document					
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document					
101.LAB	XBRL Taxonomy Extension Label Linkbase Document					
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document					

+ Indicates a management contract or any compensatory plan, contract or arrangement.

† Confidential treatment granted as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

* Filed herewith.

Item 16. Form 10-K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

CONSTELLATION PHARMACEUTICALS, INC

Date: March 10, 2020

By: /s/ Jigar Raythatha

Jigar Raythatha
President and Chief Executive Officer

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, this has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Jigar Raythatha **Jigar Raythatha**	President and Chief Executive Officer. Director (Principal Executive Officer)	March 10, 2020
/s/ Emma Reeve **Emma Reeve**	Chief Financial Officer (Principal Financial and Accounting Officer)	March 10, 2020
/s/ Mark A. Goldsmith **Mark A. Goldsmith, M.D., Ph.D.**	Chairman of the Board	March 10, 2020
/s/ James E. Audia **James E. Audia, Ph. D**	Director	March 10, 2020
/s/ Scott Braunstein **Scott Braunstein, M.D.**	Director	March 10, 2020
/s/ Steven L. Hoerter **Steven L. Hoerter**	Director	March 10, 2020
/s/ Robert Tepper **Robert Tepper, M.D.**	Director	March 10, 2020
/s/ Elizabeth G. Tréhu **Elizabeth G. Tréhu, M.D.**	Director	March 10, 2020

DESCRIPTION OF SECURITIES REGISTERED UNDER SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

The following description of the common stock, par value $0.0001 per share (the "common stock") of Constellation Pharmaceuticals, Inc. ("us," "our," "we" or the "Company"), which is the only security of the Company registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), summarizes certain information regarding the common stock in our restated certificate of incorporation, our amended and restated bylaws and applicable provisions of the Delaware General Corporation Law (the "DGCL"), and is qualified by reference to our restated certificate of incorporation and amended and restated bylaws, which are incorporated by reference as Exhibit 3.1 and Exhibit 3.2, respectively, to the Annual Report on Form 10-K.

Our authorized capital stock consists of 200,000,000 shares of common stock, $0.0001 par value per share, and 5,000,000 shares of preferred stock, $0.001 par value per share. Our common stock is registered under Section 12(b) of the Exchange Act.

Common Stock

Voting Rights. Holders of common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except when a different vote is required by law, our restated certificate of incorporation or our amended and restated bylaws.

Dividends. Holders of common stock are entitled to receive proportionately any dividends as may be declared and paid on the common stock from funds lawfully available therefor as and when determined by our board of directors, subject to any preferential dividend or other rights of any outstanding preferred stock.

Liquidation and Dissolution. In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to any preferential or other rights of any outstanding preferred stock.

Rights and Preferences. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Outstanding shares of common stock are fully-paid and non-assessable. Holders of common stock are not, and will not be, subject to any liability as stockholders.

Anti-takeover Effects of Provisions of Our Charter, Our Bylaws and Delaware law

Delaware law, our restated certificate of incorporation and our amended and restated bylaws contain, provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors

Delaware Business Combination Statute. We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless either the interested stockholder attained such status with the approval of our board of directors, the business combination is approved by our board of directors and stockholders in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Board of Directors; Removal of Directors. Our restated certificate of incorporation and our amended and restated bylaws divide our board of directors into three classes with staggered three-year terms. In addition, restated certificate of

incorporation and our amended and restated bylaws provide that directors may be removed only for cause and only by the affirmative vote of the holders of at least 75% of our shares of capital stock present in person or by proxy and entitled to vote in an election of directors or class of directors. Under restated certificate of incorporation and our amended and restated bylaws, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office. Furthermore, restated certificate of incorporation provides that the authorized number of directors may be changed only by the resolution of our board of directors. The classification of our board of directors and the limitations on the ability of our stockholders to remove directors, change the authorized number of directors and fill vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder Action; Special Meeting of Stockholders; Advance Notice Requirements for Stockholder Proposals and Director Nominations. Our restated certificate of incorporation and our bylaws provide that any action required or permitted to be taken by our stockholders at an annual meeting or special meeting of stockholders may only be taken if it is properly brought before such meeting and may not be taken by written action in lieu of a meeting. Our restated certificate of incorporation and our amended and restated bylaws also provide that, except as otherwise required by law, special meetings of the stockholders can only be called by our board of directors. In addition, our amended and restated bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors, or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities. These provisions also could discourage a third party from making a tender offer for common stock because even if the third party acquired a majority of our outstanding voting stock, it would be able to take action as a stockholder, such as electing new directors or approving a merger, only at a duly called stockholders meeting and not by written consent.

Super-Majority Voting. The DGCL provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws unless a corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our amended and restated bylaws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described above.

Issuance of Preferred Stock. Our board of directors is authorized, without further action by our stockholders, to issue up to 5,000,000 shares of preferred stock in one or more series, and to fix the designations, powers, preferences and the relative, participating, optional or other special rights, and any qualifications, limitations and restrictions of the shares of each series of preferred stock. The issuance of preferred stock could impede the completion of a merger, tender offer or other takeover attempt

Exclusive Forum Selection. Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our restated certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This exclusive forum provision will not apply to actions arising under the Securities Act of 1933, as amended, or the Exchange Act. Although our restated certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Exhibit 21.1

Subsidiaries of the Registrant

Name	Jurisdiction of Organization	Percent Ownership
Constellation Securities Corporation	Massachusetts	100%

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-8 No. 333-226291) pertaining to the Amended and Restated 2008 Stock Incentive Plan, the 2018 Equity Incentive Plan and the 2018 Employee Stock Purchase Plan of Constellation Pharmaceuticals, Inc.;
(2) Registration Statement (Form S-8 No. 333-230294) pertaining to the 2018 Equity Incentive plan of Constellation Pharmaceuticals, Inc.; and
(3) Registration Statement (Form S-3 Nos. 333-235550, 333-235417 and 333-232992) of Constellation Pharmaceuticals, Inc.

of our report dated March 10, 2020, with respect to the consolidated financial statements of Constellation Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 10, 2020

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Jigar Raythatha, certify that:

1. I have reviewed this Annual Report on Form 10-K of Constellation Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the small business issuer as of, and for, the periods presented in this report;

4. The small business issuer's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the small business issuer and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the small business issuer, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the small business issuer's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the small business issuer's internal control over financial reporting that occurred during the small business issuer's most recent fiscal quarter (the small business issuer's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the small business issuer's internal control over financial reporting; and

5. The small business issuer's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the small business issuer's auditors and the audit committee of the small business issuer's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the small business issuer's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the small business issuer's internal control over financial reporting.

Date: March 10, 2020

By: /s/ Jigar Raythatha

Jigar Raythatha
President and Chief Executive Officer

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Emma Reeve, certify that:

1. I have reviewed this Annual Report on Form 10-K of Constellation Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the small business issuer as of, and for, the periods presented in this report;

4. The small business issuer's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the small business issuer and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the small business issuer, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the small business issuer's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the small business issuer's internal control over financial reporting that occurred during the small business issuer's most recent fiscal quarter (the small business issuer's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the small business issuer's internal control over financial reporting; and

5. The small business issuer's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the small business issuer's auditors and the audit committee of the small business issuer's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the small business issuer's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the small business issuer's internal control over financial reporting.

Date: March 10, 2020

By: /s/ Emma Reeve

Emma Reeve
Chief Financial Officer

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Constellation Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Jigar Raythatha, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 10, 2020

By: /s/ Jigar Raythatha

Jigar Raythatha
President and Chief Executive Officer

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Constellation Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Emma Reeve, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 10, 2020

By: /s/ Emma Reeve

Emma Reeve
Chief Financial Officer