UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended June 30, 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 Number)**
215 First Street, Suite 200 Cambridge, Massachusetts	**02142**
(Address of principal executive offices)	**(Zip code)**

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

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 ☒

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	CNST	The Nasdaq Stock Market LLC

As of July 31, 2019, the registrant had 25,822,696 shares of common stock, $0.0001 par value per share, outstanding.

FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plan, objectives of management and expected market growth are forward-looking statements. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. Such forward-looking statements are subject to various risks and uncertainties. Accordingly, there are or will be important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. We believe these factors include but are not limited to those described under "Risk Factors" and include, among other things:

- our ongoing clinical trials, including our Phase 1b/2 clinical trial of CPI-1205 for the treatment of metastatic castration-resistant prostate cancer in combination with either enzalutamide or abiraterone acetate, which we refer to as ProSTAR; our Phase 1b/2 clinical trial of CPI-1205 for the treatment of patients with solid tumors in combination with ipilimumab or pembrolizumab, which we refer to as ORION-E; and our Phase 2 clinical trial of CPI-0610 as a monotherapy or in combination with ruxolitinib in patients with myelofibrosis, which we refer to as MANIFEST;
- 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;
- the rate and degree of market acceptance and clinical utility of our products;
- our estimates regarding the potential market opportunity for our product candidates;
- our commercialization, marketing and manufacturing 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 under the Jumpstart Our Business Startups Act of 2012.

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 Quarterly Report on Form 10-Q, particularly in the "Risk Factors" section, that we believe 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, collaborations, joint ventures or investments we may make or enter into.

You should read this Quarterly Report on Form 10-Q and the documents that we have filed as exhibits to this Quarterly Report on Form 10-Q 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 Quarterly Report on Form 10-Q are made as of the date of this Quarterly Report on Form 10-Q, 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.

Constellation Pharmaceuticals, Inc.
Table of Contents

PART I—FINANCIAL INFORMATION

Item 1. Financial Statements

CONSTELLATION PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share amounts)
(Unaudited)

	June 30, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 55,043	$ 114,592
Marketable securities	43,057	—
Prepaid expenses and other current assets	2,566	2,711
Total current assets	100,666	117,303
Property and equipment, net	1,176	1,210
Restricted cash	425	425
Operating lease, right-of-use assets	11,986	—
Total assets	$ 114,253	$ 118,938
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 6,387	$ 5,723
Accrued expenses and other current liabilities	8,607	8,937
Current portion of lease liabilities - operating lease	2,207	—
Total current liabilities	17,201	14,660
Long-term debt, net of current portion and discount	19,568	—
Operating lease liabilities, net of current portion	10,185	—
Deferred rent, net of current portion	—	118
Other long-term liabilities	115	2
Total liabilities	47,069	14,780
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized; no shares issued or outstanding at June 30, 2019 and December 31, 2018	—	—
Common stock, $0.0001 par value; 200,000,000 shares authorized at June 30, 2019 and December 31, 2018, respectively; 25,819,593 and 25,803,475 shares issued at June 30, 2019 and December 31, 2018, respectively; 25,819,423 and 25,803,135 shares outstanding at June 30, 2019 and December 31, 2018, respectively	3	3
Additional paid-in capital	341,200	337,992
Accumulated other comprehensive gain	11	—
Accumulated deficit	(274,030)	(233,837)
Total stockholders' equity	67,184	104,158
Total liabilities and stockholders' equity	$ 114,253	$ 118,938

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

CONSTELLATION PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share amounts)
(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Revenue	$ —	$ —	$ —	$ —
Operating expenses:				
Research and development	15,955	9,536	31,632	19,410
General and administrative	4,886	2,486	9,315	4,789
Total operating expenses	20,841	12,022	40,947	24,199
Loss from operations	(20,841)	(12,022)	(40,947)	(24,199)
Other income (expense):				
Interest income	652	268	1,407	377
Interest expense	(578)	(187)	(653)	(221)
Total other income (expense), net	74	81	754	156
Net loss attributable to common stockholders	$ (20,767)	$ (11,941)	$ (40,193)	$ (24,043)
Other comprehensive gain:				
Unrealized gain on marketable securities	2	—	11	—
Other comprehensive gain	$ 2	$ —	$ 11	$ —
Comprehensive loss	$ (20,765)	$ (11,941)	$ (40,182)	$ (24,043)
Net loss per share attributable to common stockholders, basic and diluted	$ (0.80)	$ (9.96)	$ (1.56)	$ (22.12)
Weighted average common shares outstanding, basic and diluted	25,809,556	1,199,164	25,807,132	1,086,697

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

CONSTELLATION PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share and per share amounts)
(Unaudited)

	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
	Shares	Amount	Shares	Amount				
Balances at December 31, 2018	—	$ —	25,803,135	$ 3	$ 337,992	$ —	$ (233,837)	$ 104,158
Stock-based compensation expense	—	—	—	—	1,313	—	—	1,313
Vesting of common stock issued upon early exercise of unvested options	—	—	85	—	—	—	—	—
Stock option exercises	—	—	3,754	—	21		—	21
Unrealized gain on marketable securities						9		9
Net loss	—	—	—	—	—	—	(19,426)	(19,426)
Balances at March 31, 2019 (unaudited)	—	$ —	25,806,974	$ 3	$ 339,326	$ 9	$ (253,263)	$ 86,075
Stock-based compensation expense	—	—	—	—	1,797	—	—	1,797
Vesting of common stock issued upon early exercise of unvested options	—	—	85	—	—	—	—	—
Stock option exercises	—	—	12,364	—	77		—	77
Unrealized gain on marketable securities						2		2
Net loss	—	—	—	—	—	—	(20,767)	(20,767)
Balances at June 30, 2019 (unaudited)	—	$ —	25,819,423	$ 3	$ 341,200	$ 11	$ (274,030)	$ 67,184

	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' 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 $132	68,500,000	68,368	—	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	585	—	—	585
Vesting of common stock issued upon early exercise of unvested options	—	—	408	—	3	—	—	3
Repayment of promissory notes issued upon early exercise of unvested options	—	—	229,357	—	290	—	—	290
Net loss	—	—	—	—	—	—	(12,102)	(12,102)
Balances at March 31, 2018 (unaudited)	187,367,177	$ 241,596	1,192,663	$ —	$ 8,957	$ —	$ (186,014)	$ (177,057)
Issuance of Series F convertible preferred stock, net of issuance costs of $12	31,250,000	31,238	—	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	687	—	—	687
Vesting of common stock issued upon early exercise of unvested options	—	—	86	—	—	—	—	—
Stock option exercises	—	—	22,088	—	96	—	—	96
Net loss	—	—	—	—	—	—	(11,941)	(11,941)
Balances at June 30, 2018 (unaudited)	218,617,177	272,834	1,214,837	$ —	$ 9,740	$ —	$(197,955)	$(188,215)

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

CONSTELLATION PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)
(Unaudited)

	Six Months Ended June 30,	
	2019	**2018**
Cash flows from operating activities:		
Net loss	$ (40,193)	$ (24,043)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization expense	364	273
Stock-based compensation expense	3,110	1,272
Non-cash interest expense	158	45
Amortization and accretion on marketable securities	(523)	—
Change in fair value of preferred stock warrant liability	—	98
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	257	(747)
Operating lease, right-of-use assets	1,461	—
Accounts payable	801	(451)
Accrued expenses and other current liabilities	(131)	1,133
Operating lease liabilities	(1,484)	—
Deferred rent	—	(47)
Other assets	—	18
Net cash used in operating activities	(36,180)	(22,449)
Cash flows from investing activities:		
Purchase of marketable securities	(63,123)	—
Purchases of property and equipment	(469)	(42)
Proceeds from maturities and sales of marketable securities	20,600	—
Net cash used in investing activities	(42,992)	(42)
Cash flows from financing activities:		
Proceeds from issuance of long-term debt	19,650	—
Payment of debt issuance costs	(125)	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	99,606
Payments on long-term debt	—	(3,510)
Proceeds from repayment of promissory notes issued upon early exercise of stock options	—	290
Payments of initial public offering costs	—	(1,855)
Proceeds from issuance of common stock upon stock option exercises	98	96
Net cash provided by financing activities	19,623	94,627
Net increase (decrease) in cash, cash equivalents and restricted cash	(59,549)	72,136
Cash, cash equivalents and restricted cash at beginning of period	115,017	16,646
Cash, cash equivalents and restricted cash at end of period	$ 55,468	$ 88,782
Supplemental disclosure of cash flow information:		
Interest paid	$ 347	$ 79
Supplemental disclosure of noncash investing and financing information:		
Purchases of property and equipment included in accounts payable	$ 41	$ —
Vesting of common stock subject to repurchase	$ —	$ 3
Deferred offering costs included in accounts payable and accrued expenses	$ —	$ 1,035

The accompanying notes are an integral part of these unaudited condensed consolidated 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. As of June 30, 2019, the Company had drawn down on the first of the four tranches and in connection with the draw down received net proceeds of $19.5 million.

The Company has incurred losses since inception, including net losses of $20.8 million and $40.2 million for the three and six months ended June 30, 2019, respectively, and $59.9 million for the year ended December 31, 2018. As of June 30, 2019, the Company had an accumulated deficit of $274.0 million. The Company expects to continue to generate operating losses in the foreseeable future. Based on the Company's current operating plan, the Company expects that its cash, cash equivalents and marketable securities at June 30, 2019 will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months from the issuance date of the interim financial statements. Management's belief with respect to its ability to fund operations is based on estimates that are subject to risks and uncertainties. If actual results are different from management's estimates, the Company may need to seek additional funding sooner than would otherwise be expected. There can be no assurance that the Company will be able to obtain additional funding on acceptable terms, if at all.

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

Unaudited Interim Consolidated Financial Information

The accompanying unaudited condensed consolidated financial statements as of June 30, 2019 and for the three and six months ended June 30, 2019 and 2018 have been prepared by the Company pursuant to the rules and regulations of the Securities and Exchange Commission ("SEC") for interim consolidated financial statements. Certain information and footnote disclosures normally included in the financial statements prepared in accordance with GAAP have been condensed or omitted pursuant to such rules and regulations. These financial statements should be read in conjunction with the Company's audited financial statements and the notes thereto included in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 (the "Annual Report").

The unaudited condensed consolidated financial statements include the accounts of Constellation Pharmaceuticals, Inc. and its wholly owned subsidiary, Constellation Securities Corporation. All intercompany transactions and balances of the subsidiary have been eliminated in consolidation. In the opinion of management, all adjustments, consisting only of normal recurring adjustments necessary for a fair statement of the Company's financial position as of June 30, 2019 and results of operations for the three and six months ended June 30, 2019 and 2018, and cash flows for the six months ended June 30, 2019 and 2018 have been made. The Company's results of operations for the three and six months ended June 30, 2019 are not necessarily indicative of the results of operations that may be expected for the year ending December 31, 2019.

Concentrations of Credit Risk and of Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and marketable securities. The Company maintains most of its cash, cash equivalents and marketable securities 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.

Summary of Significant Accounting Policies

The Company's significant accounting policies are described in Note 2, "Summary of Significant Accounting Policies," to the Consolidated Financial Statements included in the Annual Report. There have been no material changes to the significant accounting policies previously disclosed in the Annual Report other than as noted below.

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 consists of net loss and unrealized gain (losses) on available-for-sale marketable securities.

Cash, Cash Equivalents and Restricted Cash

Cash and cash equivalents consists of all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

As of June 30, 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 12). Cash, cash equivalents and restricted cash consists of the following:

	June 30, 2019	December 31, 2018
Cash and cash equivalents	$ 55,043	$ 114,592
Restricted cash	425	425
Cash, cash equivalents and restricted cash	$ 55,468	$ 115,017

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 marketable securities 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 June 30, 2019 (see Note 7) approximated fair value (a Level 3 measurement) based on interest rates currently available to the Company.

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.

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-Q.

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. This guidance will be effective for annual reporting periods beginning after December 15, 2019, including interim periods within those annual reporting periods, and early adoption is permitted. The Company is currently evaluating the potential impact that the adoption of this guidance may have on the condensed 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. For public entities, this guidance is required to be adopted for annual periods beginning after December 15, 2018, including interim periods within those fiscal years. For nonpublic entities, this guidance is effective for annual periods beginning after December 15, 2019. Early adoption is permitted for all entities, including adoption in an interim period. The Company is currently evaluating the impact that the adoption of ASU 2017-11 will have on its consolidated 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 is currently evaluating the impact that the adoption of ASU 2018-13 will have on its consolidated financial statements.

3. Fair Value of Financial Assets and Liabilities

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):

	June 30, 2019			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds included in cash and cash equivalents	$ 55,043	$ —	$ —	$ 55,043
Commercial paper	—	—	—	—
Total	$ 55,043	$ —	$ —	$ 55,043
Marketable securities:				
Corporate debt securities	$ —	$ 8,173	$ —	$ 8,173
Commercial paper	—	$ 26,899	—	26,899
Government securities	—	7,985	—	7,985
Total	$ —	$ 43,057	$ —	$ 43,057

	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.

During the three and six months ended June 30, 2019 and the year ended December 31, 2018, there were no transfers between Level 1 and Level 2. The fair value of Level 2 instruments classified as cash equivalents and marketable debt securities were determined through third-party pricing services.

4. Marketable Securities

The following table summarizes the Company's marketable securities and cash equivalents as of June 30, 2019. The Company did not hold any marketable securities as of December 31, 2018.

	June 30, 2019			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
(in thousands)				
Cash equivalents:				
Money market funds	$ 55,043	$ —	$ —	$ 55,043
Commercial paper	—	—	—	—
Total cash equivalents	$ 55,043	$ —	$ —	$ 55,043
Marketable securities:				
Corporate debt securities	$ 8,165	$ 8	$ —	$ 8,173
Commercial paper	26,899	—	—	26,899
Government securities	7,982	3	—	7,985
Total marketable securities	$ 43,046	$ 11	$ —	$ 43,057
Total cash equivalents and marketable securities	$ 98,089	$ 11	$ —	$ 98,100

5. Accrued Expenses and Other Current Liabilities

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

	June 30, 2019	December 31, 2018
Accrued employee compensation and benefits	$ 2,216	$ 2,726
Accrued external research and development expense	5,768	5,610
Accrued professional fees	289	255
Other	334	346
	$ 8,607	$ 8,937

6. Collaboration Agreement

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 six months ended June 30, 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 11).

7. 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 June 30, 2019 is $20 million. As of June 30, 2019, the Company had drawn down on the first of the four tranches, and its ability to draw down the remainder of the tranches is 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 (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 June 30, 2019, notes payable consisted of the following:

	June 30, 2019
Principal amount of term loans	$ 20,000
Debt discount current portion	—
Less: Current portion	—
Long-term debt, net of current portion	20,000
Debt discount net of current portion	(432)
Long-term debt, net of discount and current portion	$ 19,568

8. 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.

9. 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.

10. Equity

Common Stock

As of June 30, 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.

Warrants to Purchase Common Stock

As of June 30, 2019, the Company had 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
June 28, 2013	10	$ 13.22	11,354
September 30, 2014	10	$ 13.22	22,708
			95,930

11. 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 January 1, 2019 and each January 1 thereafter 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. In January 2019, the shares available for issuance under the 2018 Plan were increased by 1,032,125 shares pursuant to the annual increase described above. As of June 30, 2019, 1,789,413 shares remained available for future issuance under the 2018 Plan.

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 January 1, 2020 and 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.

Stock Option Issuances

The following is a summary of stock option activity for the three months ended June 30, 2019,

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2018	3,779,403	$ 7.78	8.80	$ 110
Granted	1,269,799	9.12		
Exercised	(16,288)	6.05		
Forfeited	(203,182)	8.81		
Outstanding as of June 30, 2019	4,829,732	$ 8.09	8.66	$ 20,279
Vested and expected to vest as of June 30, 2019	4,829,732	$ 8.09	8.66	$ 20,281
Options exercisable as of June 30, 2019	1,409,204	$ 6.72	7.71	$ 7,840

During the six months ended June 30, 2019, the Company granted options to employees, consultants and directors for the purchase of 1,269,799 shares of common stock with a weighted average exercise price of $9.12 per share and a weighted average grant-date fair value of $6.47 per share.

The Company estimated the fair value of each stock option award using the Black-Scholes option-pricing model based on the following assumptions:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Risk-free interest rate	2.06%	2.87%	2.44%	2.79%
Expected volatility	83.08%	80.85%	82.24%	80.75%
Expected dividend yield	—	—	—	—
Expected term (in years)	5.68	6.06	6.02	6.05

As of June 30, 2019, total unrecognized compensation cost related to the unvested stock-based awards was $19.7 million, which is expected to be recognized over a weighted average period of 2.93 years.

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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Research and development expenses	$ 732	$ 291	$ 1,256	$ 502
General and administrative expenses	1,065	396	1,854	770
Total	$ 1,797	$ 687	$ 3,110	$ 1,272

12. 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.

We recognize our 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 we recognized all leases with terms greater than 12 months in duration on our Condensed Consolidated Balance Sheets as right-of-use assets and lease liabilities as of January 1, 2019. We adopted the standard using the modified retrospective approach.

Upon adoption of ASC 842 on January 1, 2019, we 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 our condensed consolidated statements of operations. Prior periods are presented in accordance with ASC 840, *Leases*.

We have made certain assumptions and judgments when applying ASC 842, the most significant of which are:

- We elected the package of practical expedients available for transition which allow us 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.
- We 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, we 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, we 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.
- We use our incremental borrowing rate to calculate the present value of our lease payments, as the implicit rates in our leases are not readily determinable.

As of June 30, 2019, assets under operating lease were $12.0 million. The elements of lease expense were as follows (in thousands):

	For Six Months Ended June 30, 2019
Lease cost:	
Operating lease cost	1,465
Variable lease cost (1)	206
Total Lease cost	1,671
Other information:	
Operating cash flows used for operating leases	1,484
Operating lease liabilities arising from obtaining right-of-use assets	12,392
Weighted-average remaining lease term in years	4.0
Weighted-average discount rate	10.37%

(1) The variable lease costs for the three and six months ended June 30, 2019 include common area maintenance charges.

Future minimum lease payments under the operating lease as of June 30, 2019 are as follows (in thousands):

Year Ending December 31,	
2019	1,676
2020	3,592
2021	3,880
2022	3,997
2023	2,033
	$ 15,178
Present value adjustment	(2,786)
Present value of lease liabilities	$ 12,392

Rent expense for each of the three months ended June 30, 2019 and 2018 was $0.8 million and $0.6 million, respectively. Rent expense for each of the six months ended June 30, 2019 and 2018 was $1.5 million and $1.1 million, respectively.

13. 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 June 30, 2019, and December 31, 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 June 30, 2019, and December 31, 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 June 30, 2019 or December 31, 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 our 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. We filed an answer in March 2017. A dispositive motion is currently pending with the District Court and has yet to be decided. The plaintiff claims damages of $1.5 million. We are working with counsel and our insurer to vigorously defend our position. We believe that we have meritorious defenses, however unfavorable outcome of some amount is reasonably possible.

14. 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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Numerator:				
Net loss	$ (20,767)	$ (11,941)	$ (40,193)	$ (24,043)
Net loss attributable to common stockholders	$ (20,767)	$ (11,941)	$ (40,193)	$ (24,043)
Denominator:				
Weighted average common shares outstanding, basic and diluted	25,809,556	1,199,164	25,807,132	1,086,697
Net loss per share attributable to common stockholders, basic and diluted	$ (0.80)	$ (9.96)	$ (1.56)	$ (22.12)

The Company's potential dilutive securities 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:

	June 30,	
	2019	2018
Convertible preferred shares (as converted to common stock)	—	20,501,927
Warrants for the purchase of convertible preferred stock (as converted to common stock)	—	34,062
Warrants for the purchase of common stock	95,930	112,900
Options to purchase common stock	4,829,732	2,612,890
	4,925,662	23,261,779

15. 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 $0.1 million for each of the three months ended June 30, 2019 and 2018, respectively. The Company made matching contributions of $0.2 million for the six months ended June 30, 2019 and 2018, respectively.

Item 2. 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 in conjunction with our financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q and our Annual Report on Form 10-K for the twelve months period ending December 31, 2018, filed with the Securities and Exchange Commission, or SEC. Some of the information contained in this discussion and analysis or set forth elsewhere in this Quarterly Report on Form 10-Q, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the Risk Factors section of this Quarterly Report on Form 10-Q, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company 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 and 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.

BET Inhibitor

CPI-0610, one of our two lead product candidates, is a small molecule designed to promote anti-tumor activity by specifically inhibiting the function of extra terminal domain, or 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 myelofibrosis, or MF, a progressive hematological cancer. We are enrolling MF patients that are resistant, intolerant or have had a sub-optimal response to ruxolitinib, a second-line setting, as well as patients that are ruxolitinib naïve, a first-line setting. In the second-line setting (patients who have already been treated with ruxolitinib), we are stratifying patients for dependence on red-blood-cell, or RBC, transfusions. In transfusion-dependent patients, we aim to measure conversion to transfusion independence in addition to spleen volume reduction and symptom improvement. In non-transfusion-dependent patients, we aim to measure spleen volume reduction and symptom improvement, among other relevant parameters. We are also testing CPI-0610 in combination with ruxolitinib in a first-line setting (JAK inhibitor-naïve patients) with the aim of measuring spleen volume reduction and symptom improvement, among other relevant parameters.

We believe that interim data from MANIFEST as of April 17, 2019 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. 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. In addition to showing improvements in spleen volume and constitutional symptoms seen with current therapy, the interim data also suggested improvements in anemia, bone marrow fibrosis, and transfusion dependence.

As of April 17, 2019, we had enrolled 44 patients across three arms of the trial. We are continuing to enroll patients in this trial, at our approximately 20 clinical trial sites in the United States, Canada and Europe. We expect to provide an additional data update in the second half of 2019. Assuming that the clinical data are sufficiently positive and after consultation with the U.S. Food and Drug Administration, or the FDA, regarding acceptable endpoints and clinical trial design, we would expect to initiate a pivotal clinical trial of CPI-0610 in MF.

As of April 17, 2019, of the 44 patients enrolled in the trial, twelve patients had received 24-week assessments and 16 patients had received 12-week assessments. Below is a summary of results from the interim update across primary and secondary endpoints from the trial as of April 17, 2019:

- 14 out of 16 patients in the second-line treatment arms that were evaluable for spleen volume reduction experienced spleen volume reductions from baseline, measured by CT scan or MRI. In order for a patient to be evaluable for a spleen response, such patient must have at least one post-baseline scan or MRI. The median best on-study spleen volume change in these 16 patients was -19.2%.
- All 11 patients evaluable for total symptom scores improvement, as measured by the Myelofibrosis Symptom Assessment form, version 4.0, or MFSAF, achieved total symptom score improvements. The MFSAF is a patient-reported outcome that asks patients to rate the severity of their MF symptoms, consisting of fatigue, night sweats, pruritus, abdominal discomfort, pain, early satiety and bone pain, at its worst during the past 24 hours on a scale of zero (absent) to ten (worst imaginable).

- Of the 16 patients evaluable for symptom improvement using the Patient Global Impression of Change, or PGIC, instrument, 15 experienced symptom improvement. PGIC is an assessment of patients' perceptions of change in their myelofibrosis symptoms over time. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. Five additional patients were evaluable for PGIC (vs. MFSAF), as a baseline assessment, but were not required to obtain a PGIC score. As shown below, ten of the 16 patients reported to be either "Much Improved" or "Very Much Improved."
- There were three patients who were transfusion dependent at baseline who had been on treatment for at least 24 weeks. Two of these patients achieved transfusion independence for at least 24 weeks. Each of these two patients also experienced improvements in hemoglobin and platelets during the period of transfusion independence.
- Six out of 10 patients evaluable for evidence of morphological change in bone marrow fibrosis experienced improvement of at least one point in a scale of 0-3 as of April 17, 2019. Quantification of bone marrow cellularity was scored to one of four grade categories (0, 1, 2, 3) based on review by a pathologist. Patients must have had a baseline as well as at least one post-baseline assessment to be eligible for bone marrow evaluation. In addition, five patients showed improvements in bone marrow fibrosis, including one with a two-point improvement, and one additional patient showed improvement as measured by reticulin staining.

As of April 17, 2019, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated. A total of five patients discontinued treatment with CPI-0160. Three patients discontinued treatment due to a serious adverse event: one patient discontinued due to Grade 3 squamous cell carcinoma that was assessed as unrelated to CPI-0610 and related to ruxolitinib; one patient discontinued due to Grade 4 depression, which was assessed as not related to either CPI-0610 or ruxolitinib; and one patient discontinued due to Grade 5 (death) acute kidney injury, which was assessed as unlikely related to CPI-0610 and unlikely related to ruxolitinib. The acute kidney injury event was likely related to the concomitant use of other medications and possibly due to progression of disease.

The most commonly reported side effects, which occurred in more than 10% of patients, were diarrhea, vomiting, upper respiratory tract infection, headache, epistaxis, fatigue, dysgeusia, cough and pruritis. In the second-line combination arm, Grade 3 or greater treatment-emergent adverse events, or TEAEs, included thrombocytopenia, anemia and decreased platelet counts, each of which was reported in two patients. Additional Grade 3 TEAEs in the combination arm included neutropenia, increase in blood creatine, diarrhea, vomiting, nausea, dehydration, hyponatremia, acute kidney injury, proteinuria, fatigue, depression and pneumonia, each of which occurred in one patient. In advanced myelofibrosis, thrombocytopenia is a concern for BET inhibitors. In MANIFEST, as of April 17, 2019, CPI-0610 monotherapy has demonstrated non-cumulative and manageable thrombocytopenia, with no Grade 3 thrombocytopenia reported. The combination of CPI-0610 and ruxolitinib has shown a non-cumulative, manageable and mostly reversible asymptomatic thrombocytopenia.

We have begun planning for potential pivotal trials with CPI-0610, and we anticipate providing a further update from ruxolitinib-resistant and first-line patients in the fourth quarter 2019.

EZH2 Franchise

CPI-1205, our other lead product candidate, is a small molecule designed to promote anti-tumor activity by specifically inhibiting enhancer of zeste homolog 2, or 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 metastatic castration-resistant prostate cancer, or mCRPC. We are currently conducting the Phase 2 portion of an open-label Phase 1b/2 clinical trial of CPI-1205 for the treatment of mCRPC in combination with the androgen receptor signaling inhibitors enzalutamide (marketed as Xtandi®) or abiraterone acetate (marketed as Zytiga®), a clinical trial that we refer to as the ProSTAR trial. Abiraterone acetate is dosed with prednisone, which is the current clinical practice.

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. The purpose of the use of cobicistat is to block CYP3A4, which we evaluated 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 a 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 (PSA) reductions, circulating tumor cell reductions, and objective responses by response evaluation criteria in solid tumors (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%. Patients being treated with abiraterone after enzalutamide or with enzalutamide after abiraterone historically 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 (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. 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. We plan to provide an update for ProSTAR in the fourth quarter of 2019 and to provide additional data in early 2020.

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 we are targeting with CPI-1205 or that have been targeted by other EZH2 inhibitors. 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 that CPI-0209 may have broad application in large patient populations across several solid tumors. In June 2019, we submitted an investigational new drug application, or IND, to advance CPI-0209 into clinical trials for the treatment of solid tumors and the IND has been accepted by the FDA. We are preparing to initiate a Phase 1 trial of CPI-0209 in a range of solid tumors.

The Company anticipates achieving the following milestones during the second half of 2019:

- provide a data update from the MANIFEST study for approximately 40 ruxolitinib-resistant patients, including transfusion-independence conversion data from about 16 patients;
- present the first data from the MANIFEST study in first-line disease in 10-15 JAK-inhibitor-naïve patients;
- dose the first patients in a Phase 1 clinical trial of CPI-0209; and
- provide an update from the ProSTAR study across various patient contexts.

Financial Overview

As of June 30, 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 initial public offering, or IPO, completed in July 2018. 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 $20 million and may borrow up to an additional $20 million subject to certain limitations. 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 three and six months ended June 30, 2019, we reported a net loss of $20.8 million and $40.2 million, respectively. As of June 30, 2019, we had an accumulated deficit of $274.0 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next few 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 Phase 2 clinical trial of CPI-0610 as a monotherapy or in combination with ruxolitinib in patients with myelofibrosis, which we refer to as the MANIFEST trial, and our Phase 1b/2 clinical trial of CPI-1205 for the treatment of metastatic castration-resistant prostate cancer in combination with either enzalutamide or abiraterone acetate, which we refer to as the ProSTAR trial;
- initiate a Phase 1 clinical trial of CPI-0209, our second-generation EZH2 inhibitor;
- advance our clinical-stage product candidates from mid-stage trials into later-stage trials;
- continue research and development related to 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 the 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 June 30, 2019, we had cash, cash equivalents and marketable securities of $98.1 million. We expect that our existing cash, cash equivalents and marketable securities will enable us to fund our planned operating expenses and capital expenditure requirements until late third quarter of 2020. 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.

To date, our revenue has been derived from our license and collaboration arrangement with Genentech, Inc. and F. Hoffmann-La Roche Ltd., collectively referred to as Genentech, under which we licensed certain technology to Genentech and performed certain specified services. We completed our performance obligations under the collaboration arrangement in 2015 and we have not recognized revenue from Genentech since 2015. We are entitled to future milestone and royalty payments from Genentech if Genentech pursues further development of the technology licensed from us under the collaboration arrangement and if Genentech achieves specified development and sales-based milestones relating to such licensed technology. We cannot provide assurance as to the timing of milestone or royalty payments or if we will ever receive such payments from Genentech.

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 under 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. No funding was received from LLS during the six months ended June 30, 2019. During the six months ended June 30, 2018, funding by LLS of research and development expenses of $0.2 million, was recorded as a reduction of our research and development expenses.

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 sale of Series F preferred stock, the net proceeds from our IPO and net proceeds from the Hercules Loan Agreement.

Interest Expense

For the three and six months ended June 30, 2019, interest expense consists of interest expense on outstanding borrowings under the Hercules Loan Agreement, as well as amortization of debt discount and debt issuance costs.

For the three and six months ended June 30, 2018, 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, 2018, we had U.S. federal and state net operating loss carryforwards of $224.5 million and $221.6 million, respectively, which may be available to offset future income tax liabilities and begin to expire in 2028. As of December 31, 2018, we also had U.S. federal and state research and development tax credit carryforwards of $8.8 million and $3.5 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 Three Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the three months ended June 30, 2019 and 2018:

	Three Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	15,955	9,536	6,419
General and administrative	4,886	2,486	2,400
Total operating expenses	20,841	12,022	8,819
Loss from operations	(20,841)	(12,022)	(8,819)
Other income (expense):			
Interest income	652	268	384
Interest expense	(578)	(187)	(391)
Total other income (expense), net	74	81	(7)
Net loss	$ (20,767)	$ (11,941)	$ (8,826)

Research and Development Expenses

	Three Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Direct research and development expenses by program:			
CPI-1205	$ 5,123	$ 2,340	$ 2,783
CPI-0610	3,145	802	2,343
CPI-0209	580	679	(99)
Preclinical pipeline	827	572	255
Unallocated expenses:			
Personnel related (including stock-based compensation)	4,249	3,139	1,110
Laboratory supplies and consumables	529	628	(99)
Facility related and other	1,502	1,376	126
Total research and development expenses	$ 15,955	$ 9,536	$ 6,419

Research and development expenses were $16.0 million for the three months ended June 30, 2019 compared to $9.5 million for the three months ended June 30, 2018. The increase in costs related to our CPI-1205 program was primarily due to increased enrollment in our ProStar trial in the second quarter of 2019 as well as the timing of CMC campaigns. The increase in costs related to our CPI-0610 program was primarily due to increased enrollment in our MANIFEST trial in the second quarter of 2019. The increase in preclinical pipeline expenses was primarily due to the stage of development of our current pipeline candidates.

The increase in personnel related costs was primarily due to an increase in stock-based compensation expense and overall compensation in our research and development function. Personnel-related costs for the three months ended June 30, 2019 and 2018 included stock-based compensation expense of $0.7 million and $0.3 million, respectively.

General and Administrative Expenses

	Three Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Personnel related (including stock-based compensation)	$ 2,762	$ 1,265	$ 1,497
Professional and consultant fees	1,157	726	431
Facility related and other	967	495	472
Total general and administrative expenses	$ 4,886	$ 2,486	$ 2,400

General and administrative expenses for the three months ended June 30, 2019 were $4.9 million, compared to $2.5 million for the three months ended June 30, 2018. The increase in personnel related costs was primarily due to increased headcount and increased stock-based compensation expense. Personnel-related costs for the three months ended June 30, 2019 and 2018, included stock-based compensation expense of $1.1 million and $0.4 million, respectively. Facility related and other costs increased by $0.5 million primarily due to the new facility leases, franchise taxes, insurance expense and ongoing business activities, partially due to increased costs to operate as a public company.

Other Income (Expense)

Interest Income

Interest income increased to $0.7 million for the three months ended June 30, 2019, primarily due to interest income associated with our marketable securities. Interest income was $0.3 million for the three months ended June 30, 2018, primarily from our interest bearing cash and cash equivalent accounts.

Interest Expense

Interest expense was $0.6 million for the three months ended June 30, 2019 and consisted primarily of cash and non-cash interest related to the Hercules Loan Agreement. Interest expense was $0.2 million for the three months ended June 30, 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 Six Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the six months ended June 30, 2019 and 2018:

	Six Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	31,632	19,410	12,222
General and administrative	9,315	4,789	4,526
Total operating expenses	40,947	24,199	16,748
Loss from operations	(40,947)	(24,199)	(16,748)
Other income (expense):			
Interest income	1,407	377	1,030
Interest expense	(653)	(221)	(432)
Total other income (expense), net	754	156	598
Net loss	$ (40,193)	$ (24,043)	$ (16,150)

Research and Development Expenses

	Six Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Direct research and development expenses by program:			
CPI-1205	$ 10,281	$ 5,232	$ 5,049
CPI-0610	5,623	1,628	3,995
CPI-0209	1,696	1,314	382
Preclinical pipeline	1,648	1,079	569
Unallocated expenses:			
Personnel related (including stock-based compensation)	8,462	6,283	2,179
Laboratory supplies and consumables	993	1,298	(305)
Facility related and other	2,929	2,576	353
Total research and development expenses	$ 31,632	$ 19,410	$ 12,222

Research and development expenses were $31.6 million for the six months ended June 30, 2019 compared to $19.4 million for the six months ended June 30, 2018. The increase in costs related to our CPI-1205 program was primarily due to increased enrollment in our ProStar trial in the six months ended June 30, 2019 as well as the timing of CMC campaigns. The increase in costs related to our CPI-0610 program was primarily due to increased enrollment in our MANIFEST trial in the six months ended June 30, 2019. The increase in costs related to our second-generation EZH2 inhibitor CPI-0209 program in the six months ended June 30, 2019 was primarily due to continuation of process chemistry, IND-enabling study expenses and the start-up expenses related to our anticipated Phase 1 clinical study. The increase in preclinical pipeline expenses was primarily due to the stage of development of our current pipeline candidates.

The increase in personnel related costs was primarily due to an increase in stock-based compensation expense and overall compensation in our research and development function. Personnel-related costs for the six months ended June 30, 2019 and 2018 included stock-based compensation expense of $1.3 million and $0.5 million, respectively. The decrease in laboratory supplies and consumables was primarily a decrease in reagent spend due to timing of projects.

General and Administrative Expenses

	Six Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Personnel related (including stock-based compensation)	$ 5,257	$ 2,475	$ 2,782
Professional and consultant fees	2,154	1,336	818
Facility related and other	1,904	978	926
Total general and administrative expenses	$ 9,315	$ 4,789	$ 4,526

General and administrative expenses for the six months ended June 30, 2019 were $9.3 million, compared to $4.8 million for the six months ended June 30, 2018. The increase in personnel related costs was primarily due to increased headcount and increased stock-based compensation expense. Personnel-related costs for the six months ended June 30, 2019 and 2018, included stock-based compensation expense of $1.9 million and $0.8 million, respectively. The increase in professional and consulting fees is primarily due to increase in marketing, PR and accounting fees. Facility related and other costs increased by $0.9 million primarily due to the new facility leases, franchise taxes, insurance expense and ongoing business activities, partially due to increased costs to operate as a public company.

Other Income (Expense)

Interest Income

Interest income increased to $1.4 million for the six months ended June 30, 2019, primarily due to interest income associated with our marketable securities. Interest income was $0.4 million for the six months ended June 30, 2018, primarily from our interest-bearing cash and cash equivalent accounts.

Interest Expense

Interest expense was $0.7 million for the six months ended June 30, 2019 and consisted primarily of cash and non-cash interest related to the Hercules Loan Agreement. Interest expense was $0.2 million for the six months ended June 30, 2018 and consisted primarily of cash and non-cash interest related to the 2016 Loan Agreement, which was paid off in July 2018.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. As of June 30, 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 the IPO completed in July 2018. On March 20, 2019, the Company entered into a Loan and Security Agreement (the Loan Agreement) to provide up to $40.0 million in funding, to be made available in four tranches. As of June 30, 2019, we had drawn down on the first of the four tranches and in connection with the draw down received net proceeds of $19.5 million. As of June 30, 2019, we had cash, cash equivalents and marketable securities of $98.1 million.

Cash Flows

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

	Six Months Ended June 30,	
	2019	2018
	(in thousands)	
Cash used in operating activities	$ (36,180)	$ (22,449)
Cash used in investing activities	(42,992)	(42)
Cash provided by financing activities	19,623	94,627
Net increase (decrease) in cash, cash equivalents and restricted cash	$ (59,549)	$ 72,136

Operating Activities

During the six months ended June 30, 2019, net cash used in operating activities was $36.2 million, primarily resulting from our net loss of $40.2 million, partially offset by changes in our operating assets and liabilities of $0.9 million and net non-cash expense of $3.1 million. Changes in our operating assets and liabilities for the six months ended June 30, 2019 consisted primarily of a $0.8 million increase in accounts payable, and $0.2 million increase in prepaid expense and other current assets, partially offset by $0.1 million decrease in accrued expenses and other current liabilities.

During the six months ended June 30, 2018, net cash used in operating activities was $22.4 million, primarily resulting from our net loss of $24.0 million and changes in our operating assets and liabilities of $0.1 million, partially offset by net non-cash expense of $1.7 million. Changes in our operating assets and liabilities for the six months ended June 30, 2018 consisted primarily of a $0.7 million decrease in prepaid expenses and other current assets and $0.5 million decrease in accounts payable, partially offset by a $1.1 million increase in accrued expenses and other current liabilities.

Investing Activities

During the six months ended June 30, 2019 net cash used in investing activities was $43.0 million, due to cash investment in marketable securities. During the six months ended June 30, 2018, net cash used in investing activities was less than $0.1 million, due to purchases of property and equipment, related equipment and software purchases as we expanded our discovery activities.

Financing Activities

During the six months ended June 30, 2019, net cash provided by financing activities was $19.6 million, consisting primarily of net proceeds from the issuance of notes payable related to the Loan Agreement with Hercules.

During the six months ended June 30, 2018, net cash provided by financing activities was $94.6 million, consisting primarily of net proceeds from the issuance of our Series F preferred stock of $99.6 million, partially offset by payments of $3.5 million on long-term debt under the 2016 Loan Agreement and $1.9 million of payments of IPO costs.

Loan and Security Agreement

We previously had outstanding amounts due under a 2016 Loan Agreement of $11.8 million. 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, pursuant to which we may borrow up to an aggregate principal amount of $40.0 million, to be paid in four tranches, under a term loan facility. As of June 30, 2019, we had drawn down on the first of the four tranches, and our ability to draw down the remainder of the tranches is 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 (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 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 any 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 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 of the Company. If we fail to make payments when due, breach any operational covenant, or have 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 the IPO, we expect 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;
- 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 June 30, 2019, we had cash, cash equivalents and marketable securities of $98.1 million. We expect that our existing cash, cash equivalents and marketable securities, will enable us to fund our planned operating expenses and capital expenditure requirements until late third quarter of 2020. We have based these estimates 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 June 30, 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	4 to 5 Years	More Than 5 Years
	(in thousands)				
Operating lease commitment (1)	$ 15,178	$ 3,360	$ 11,818	$ —	$ —
Debt obligations (2)	26,660	1,648	11,886	13,126	—
Total	$ 41,838	$ 5,008	$ 23,704	$ 13,126	$ —

(1) Amounts in table reflects payments due for our lease of office and laboratory space in Cambridge, Massachusetts under an 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 June 30, 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 June 30, 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 June 30, 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 financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that of our critical accounting policies described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations – Critical Accounting Policies and Significant Judgments and Estimates" in our Annual Report on Form 10-K for the year ended December 31, 2018 (the "Annual Report"), the following involve the most judgment and complexity:

- accrued research and development expenses;
- stock-based compensation;
- valuation of warrants to purchase preferred stock; and
- valuation of preferred stock tranche liability.

Accordingly, we believe the policies set forth above are critical to fully understanding and evaluating our financial condition and results of operations. If actual results or events differ materially from the estimates, judgments and assumptions used by us in applying these policies, our reported financial condition and results of operations could be materially affected. There have been no significant changes to our critical accounting policies from those described in the Annual Report.

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 Quarterly Report on Form 10-Q.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

As of June 30, 2019, we had cash, cash equivalents and marketable securities of $98.1 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.

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.

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 4. 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 June 30, 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 June 30, 2019 at the reasonable assurance level.

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) during the three months ended June 30, 2019 that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II – OTHER INFORMATION

Item 1. 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 our 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. We filed an answer in March 2017. A dispositive motion is currently pending with the District Court and has yet to be decided. The plaintiff claims damages of $1.5 million. We are working with counsel and our insurer to vigorously defend our position. We believe that we have meritorious defenses however an unfavorable outcome of some amount is reasonably possible.

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 Quarterly Report on Form 10-Q 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 $20.8 million and $40.2 million for the three and six months ended June 30, 2019, respectively, and $59.9 million for the year ended December 31, 2018. As of June 30, 2019, we had an accumulated deficit of $274.0 million. To date, we have financed our operations primarily through our initial public offering, sales of our preferred stock, payments received in connection with collaboration and research agreements and borrowings under loan agreements. 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 our Phase 1b/2 clinical trial of CPI-1205, which we refer to as the ProSTAR trial, and our Phase 2 clinical trial of CPI-0610, which we refer to as MANIFEST;
- prepare for a Phase 1 clinical trial of CPI-0209, our second-generation EZH2 inhibitor;
- advance our clinical-stage product candidates into later stage trials;
- 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 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.

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 fund
eliminate our product development progr

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 and our Phase 2 clinical trial of CPI-0610 and initiate a Phase 1 clinical trial of CPI-0209; 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 and Phase 2 clinical trial of CPI-0610;
- the scope, progress, results and costs of discovery research, preclinical development, laboratory testing and clinical trials for our other product candidates, including initiating our Phase 1 clinical trial of CPI-0209;
- 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 June 30, 2019, we had cash, cash equivalents and marketable securities of approximately $98.1 million. We expect that our existing cash, cash equivalents and marketable securities as of June 30, 2019, will enable us to fund our planned operating expenses and capital expenditure requirements until late third quarter of 2020. 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 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 us 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 pa
which could materially and adversely aff

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 $20.0 million to date and $20.0 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 June 30, 2019, we had $20.0 million of borrowings outstanding under the Loan Agreement with Hercules Capital, Inc. $20.0 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 recently reported that a pediatric patient in its Phase 1 clinical trial of an EZH2 inhibitor had developed a secondary lymphoma 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 preclinical or 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, which studies are currently ongoing, 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. Further, 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 only have two product candidates in clinical trials that we are developing, CPI-1205 for the treatment of metastatic castration-resistant prostate cancer, or mCRPC, and CPI-0610 for the treatment of myelofibrosis, or MF. We plan to initiate clinical trials on our second generation EZH2 inhibitor CPI-0209 product candidate. 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 experience in epigenetics 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.

A key element of our strategy is 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. 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 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, 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., BMS, CellCentric Ltd., Celgene Corporation, 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. These facilities may also be affected by natural disasters, such as floods or fire, or such 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, some of our clinical trials are conducted outside of the United States. Changes in import/export regulations or practices could impact our ability to 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, in January 2017, a participant dosed in our Phase 1 clinical trial of CPI-0610 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, related to alleged psychological injuries resulting from the use of CPI-0610. The plaintiff is seeking damages of $1.5 million and alleges that the trial protocols did not adequately inform the plaintiff of the risks of psychosis and that the plaintiff was misled into believing that the Phase 1 clinical trial participation was with a product that had already proven efficacious. We filed an answer in March 2017. While we believe we have meritorious defenses, expect insurance to cover any damages as a result of this claim and do not deem this litigation to be material, it could divert management's attention and resources, and result in harm to our reputation or any of the other results described below.

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 and Phase 2 clinical trial of CPI-0610 and plan to rely on third-party clinical research organizations or third-party research collaboratives to conduct our planned clinical trials. We do not plan to independently conduct clinical trials of our other product candidates. 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 or personnel, 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. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers 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 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-1205, CPI-0610 and 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 are currently party to a license and collaboration agreement with Genentech, Inc., or Genentech, and F. Hoffmann-La Roche Ltd, or Roche, pursuant to which we have granted Genentech and Roche exclusive licenses to develop and commercialize products directed to a certain target in return for potential milestone and/or royalty payments. Pursuant to this license and collaboration agreement, we have, and in connection with any other such arrangements we enter into with any third parties in the future, 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 as RE47428.

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.

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 a 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. On March 29, 2017, the United Kingdom formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom had a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the European Union. If no formal withdrawal agreement can be reached between the United Kingdom and the European Union, then it is expected that the United Kingdom's membership of the European Union would automatically terminate on the deadline, which was initially March 29, 2019. That deadline has been extended to October 31, 2019 to allow the parties additional time to negotiate a withdrawal agreement, which has proven to be extremely difficult to date. Discussions between the United Kingdom and the European Union will continue to focus on withdrawal issues and transition agreements. However, limited progress to date in these negotiations and ongoing uncertainty within the government of the United Kingdom sustains the possibility of the United Kingdom leaving the European Union without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of nalbuphine ER or any future product candidate in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced 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 $5,500 to $11,000 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 US Court of Appeals for the Fifth Circuit considering this judgment that it does not oppose the lower court's ruling. To that end, on May 1, 2019, the Justice Department filed a brief asking the Court to strike down the entirety of the ACA. Thereafter, on July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. In those arguments, the Trump administration argued in support of upholding the lower court decision. 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. 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. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

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 principal stockholders, if they choose to act together, have the ability to control all matters submitted to stockholders for approval.

As of July 31, 2019, our executive officers, directors and affiliated stockholders, in the aggregate, owned shares representing approximately 44.2% of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management 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 July 31, 2019, the closing price of our common stock ranged from a high of $13.64 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. In July 2018, we 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 and the lock-up agreements entered into in connection with our initial public offering.

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

We are an "emerging growth company," as defined in the 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. 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 will be 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 2. Unregistered Sales of Equity Securities and Use of Proceeds

None.

Use of Proceeds from Initial Public Offering

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 had not used any of the net proceeds from the IPO as of June 30, 2019 as we have continued to fund operations from proceeds received through our preferred stock financings. We have invested the unused net proceeds from the offering in money market accounts and marketable securities.

Item 6. Exhibits

Exhibit Number	Description of Exhibit
10.1*	Fifth Amendment to Lease, dated as of June 17, 2019, between the Registrant and ARE-MA Region No. 38, LLC
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act, 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
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

* Filed herewith
\+ Furnished herewith

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

CONSTELLATION PHARMACEUTICALS, INC.

Date: August 7, 2019

By: /s/ Jigar Raythatha
Jigar Raythatha
President and Chief Executive Officer
(Principal Executive Officer)

Date: August 7, 2019

By: /s/ Emma Reeve
Emma Reeve
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 10.1

FIFTH AMENDMENT TO LEASE

THIS FIFTH AMENDMENT TO LEASE (this "**Fifth Amendment**") is made as of June ___, 2019, by and between **ARE-MA REGION NO. 38, LLC**, a Delaware limited liability company ("**Landlord**"), and **CONSTELLATION PHARMACEUTICALS, INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A. Landlord and Tenant are parties to that certain Lease Agreement dated as of February 5, 2010, as amended by that certain First Amendment to Lease dated as of October 25, 2011, as further amended by that certain Second Amendment to Lease dated as of October 18, 2013, as further amended by that certain letter agreement dated as of September 30, 2015, as further amended by that certain Third Amendment to Lease dated as of September 26, 2016, and as further amended by that certain Fourth Amendment to Lease dated as of September 28, 2018 (the "Fourth Amendment") (as amended, the "Lease"). Pursuant to the Lease, Tenant leases certain "Premises" containing approximately 47,546 rentable square feet, consisting of (i) a portion of the 2nd floor of the Building, containing approximately 36,309 rentable square feet (the "Original Premises"), and (ii) a portion of the 4th floor of the Building consisting of (x) Suite 401-S containing approximately 6,815 rentable square feet, and (y) Suite 430 containing approximately 4,422 rentable square feet (collectively, the "Expansion Premises"), in that certain building located at 215 First Street, Cambridge, Massachusetts (the "Building"). The Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. The Term of the Lease with respect to the Original Premises is scheduled to expire on June 30, 2020, and the Term of the Lease with respect to the Expansion Premises is scheduled to expire on March 6, 2022.

C. Landlord and Tenant desire, subject to the terms and conditions set forth below, to amend the Lease to, among other things, extend the Term of the Lease with respect to the entire Premises through June 30, 2023 (the "**Fifth Amendment Expiration Date**").

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Term**. The Term of the Lease with respect to the entire Premises (i.e., the Original Premises and the Expansion Premises) is hereby extended through the Fifth Amendment Expiration Date. Except as otherwise expressly provided in Section 3 below, Tenant's occupancy of the Premises through the Fifth Amendment Expiration Date shall be on an "as-is" basis and Landlord shall have no obligation to provide any tenant improvement allowance or to make any alterations to the Premises.

2. **Base Rent**.

a. **Original Premises.** Tenant shall continue to pay Base Rent for the Original Premises as provided for in the Lease through June 30, 2020. Commencing on July 1, 2020, Tenant shall commence paying Base Rent for the Original Premises in the amount of $81.00 per rentable square foot of the Original Premises per year. Base Rent payable with respect to the Original Premises shall be increased on each subsequent July 1st through the Fifth Amendment Expiration Date (each, an "**Original Premises Adjustment Date**") by 3% by multiplying the Base Rent payable with respect to the Original Premises immediately before such Original Premises Amendment Adjustment Date by 3% and adding the resulting amount to the Base Rent payable with respect to the Original Premises immediately before such Original Premises Adjustment Date. For the avoidance of doubt, the parties agree that Base Rent with respect to the Original Premises (i) is currently payable in the annual amount of $2,430,887.55 (through June 30, 2019), (ii) shall be payable in the annual amount of $2,503,814.18 for the period of July 1, 2019 through June 30, 2020, and (iii) shall be payable in the following amounts for the period of July 1, 2020 through June 30, 2023:

Lease Period	Annual Base Rent	Monthly Base Rent Payment
July 1, 2020 – June 30, 2021	$2,941,029.00	$245,085.75
July 1, 2021 – June 30, 2022	$3,029,259.87	$252,438.32
July 1, 2022 – June 30, 2023	$3,120,137.67	$260,011.47

b. **Expansion Premises**. Tenant shall continue to pay Base Rent with respect to the Expansion Premises as provided under the Lease through February 28, 2022. Commencing on March 1, 2022, and thereafter on each subsequent March 1st during through the Fifth Amendment Expiration Date (each, an "**Expansion Premises Adjustment Date**"), Base Rent payable with respect to the Expansion Premises shall be increased by 3% my multiplying the Base Rent payable with respect to the Expansion Premises immediately before such Expansion Premises Adjustment Date by 3% and adding the resulting amount to the Base Rent payable with respect to the Expansion Premises immediately before such Expansion Premises Adjustment Date. For the avoidance of doubt, the parties agree that Base Rent with respect to the Expansion Premises for the period commencing on the Expansion Premises Rent Commencement Date (March 7, 2019) through June 30, 2023 shall be paid in the following amounts:

Lease Period	Annual Base Rent	Monthly Base Rent Payment
March 7, 2019 – March 6, 2020	$848,393.50	$70,699.46
March 7, 2020 – March 6, 2021	$873,845.31	$72,820.44
March 7, 2021 – February 28, 2022	$900,060.67	$75,005.06
March 1, 2022 – February 28, 2023	$927,062.49	$77,255.21
March 1, 2023 – June 30, 2023	$954,874.36	$79,572.86

3. **Original Premises TI Allowance**. Landlord shall make available to Tenant a tenant improvement allowance of up to $15.00 per rentable square foot of the Original Premises, or $544,635 in the aggregate (the "**Original Premises TI Allowance**") for the design and construction (including Tenant's project management fees) of fixed and permanent improvements desired by and performed by Tenant and reasonably acceptable to Landlord in the Original Premises (the "**Original Premises Improvements**"), which Original Premises Improvements shall be constructed pursuant to a scope of work reasonably acceptable to Landlord and Tenant. The Original Premises TI Allowance shall be available only for the design and construction of the Original Premises Improvements (including Tenant's project management fees). Tenant acknowledges that upon the expiration of the Term of the Lease, the Original Premises Improvements shall become the property of Landlord and may not be removed by Tenant. Except for the Original Premises TI Allowance, Tenant shall be solely responsible for all of the costs of the Original Premises Improvements. The Original Premises Improvements shall be treated as Alterations and shall be undertaken pursuant to Section 12 of the Lease. The contractor for the Original Premises Improvements shall be selected by Tenant, subject to Landlord's approval, which approval shall not be unreasonably withheld, conditioned or delayed. Prior to the commencement of the Original Premises Improvements, Tenant shall deliver to Landlord a copy of any contract with Tenant's contractors, and certificates of insurance from any contractor performing any part of the Original Premises Improvements evidencing industry standard commercial general liability, automotive liability, "builder's risk", and workers' compensation insurance. Tenant shall cause the general contractor to provide a certificate of insurance naming Landlord, Alexandria Real Estate Equities, Inc., and Landlord's lender (if any) as additional insureds for the general contractor's liability coverages required above.

During the course of design and construction of the Original Premises Improvements, Landlord shall reimburse Tenant for the cost of the Original Premises Improvements once a month against a draw request in Landlord's standard form, containing evidence of payment of the applicable costs and such certifications, lien waivers (including a conditional lien release for each progress payment and unconditional lien releases for the prior month's progress payments), inspection reports and other matters as Landlord customarily and reasonably obtains, to the extent of Landlord's approval thereof for payment, no later than 30 days following receipt of such draw request. Upon completion of the Original Premises Improvements (and prior to any final disbursement of the Original Premises TI Allowance) Tenant shall deliver to Landlord the following items: (i) sworn statements setting forth the names of all contractors and subcontractors who did work on the Original Premises Improvements and final lien waivers from all such contractors and subcontractors; and (ii) "as built" plans for the Original Premises Improvements. Notwithstanding the foregoing, if the cost of the Original Premises Improvements exceeds the Original Premises TI Allowance, Tenant shall be required to pay such excess in full prior to Landlord having any obligation to fund any remaining portion of the Original Premises TI Allowance. The Original Premises TI Allowance shall only be available for use by Tenant for the construction of the Original Premises Improvements until the date that is 12 months after the date of this Fifth Amendment (the "**Outside Original Premises TI Allowance Date**"). Any portion of the Original Premises TI Allowance which has not been properly requested by Tenant from Landlord on or before the Outside Original Premises TI Allowance Date shall be forfeited and shall not be available for use by Tenant.

4. **Brokers**. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this Fifth Amendment and that no Broker brought about this transaction, other than CBRE. Landlord and Tenant each hereby agrees to indemnify and hold the other harmless from and against any claims by any Broker, other than CBRE, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this leasing transaction. Landlord shall pay any commission due to CBRE pursuant to a separate written agreement.

5. **OFAC**. Tenant and, to Tenant's knowledge, all beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the Term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List, or the Sectoral Sanctions Identification List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

6. **Miscellaneous**.

a. This Fifth Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This Fifth Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. This Fifth Amendment is binding upon and shall inure to the benefit of the parties hereto and their respective successors and assigns.

c. This Fifth Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Fifth Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this Fifth Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this Fifth Amendment. In the event of any conflict between the provisions of this Fifth Amendment and the provisions of the Lease, the provisions of this Fifth Amendment shall prevail. Whether or not specifically amended by this Fifth Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this Fifth Amendment.

[Signatures are on the next page.]

IN WITNESS WHEREOF, the parties hereto have executed this Fifth Amendment as of the day and year first above written.

TENANT:

CONSTELLATION PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____

Its: _____

LANDLORD:

ARE-MA REGION NO. 38, LLC,
a Delaware limited liability company

By: Alexandria Real Estate Equities, L.P.,
a Delaware limited partnership, managing member

By: ARE-QRS Corp., a Maryland corporation, general partner

By: _____

Its: _____

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 Quarterly Report on Form 10-Q 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 registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer 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)) for the registrant 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 registrant, 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) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

Date: August 7, 2019

By: /s/ Jigar Raythatha
Jigar Raythatha
President and Chief Executive Officer
(Principal 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 Quarterly Report on Form 10-Q 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 registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer 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)) for the registrant 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 registrant, 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) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

Date: August 7, 2019

By: /s/ Emma Reeve
Emma Reeve
Chief Financial Officer
(Principal Financial and Accounting 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 Quarterly Report on Form 10-Q of Constellation Pharmaceuticals, Inc. (the "Company") for the period ended June 30, 2019, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jigar Raythatha, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(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 results of operations of the Company.

Date: August 7, 2019

By: /s/ Jigar Raythatha
Jigar Raythatha
President and Chief Executive Officer
(Principal 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 Quarterly Report on Form 10-Q of Constellation Pharmaceuticals, Inc. (the "Company") for the period ended June 30, 2019, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Emma Reeve, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to her knowledge:

(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 results of operations of the Company.

Date: August 7, 2019

By: /s/ Emma Reeve
Emma Reeve
Chief Financial Officer
(Principal Financial and Accounting Officer)