UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 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, 2018
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 001-36193

Trevena, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**26-1469215**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
955 Chesterbrook Boulevard, Suite 200 Chesterbrook, PA	**19087**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(610) 354-8840**

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or 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 ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐
Emerging growth company ☒	

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

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practical date.

Common Stock, $0.001 par value	Shares outstanding as of July 31, 2018: 76,082,280

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. ☒

TABLE OF CONTENTS

Cautionary Note Regarding Forward-Looking Statements

This Quarterly Report on Form 10-Q (this "Quarterly Report") contains forward-looking statements that involve substantial risks and uncertainties. The forward-looking statements are contained principally in the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations," but also are contained elsewhere in this Quarterly Report, as well as in sections such as "Risk Factors" that are incorporated by reference into this Quarterly Report from our most recent Annual Report on Form 10-K (the "Annual Report"). In some cases, you can identify forward-looking statements by the words "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue" and "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Quarterly Report, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Forward-looking statements include statements about:

- our plans to develop and potentially commercialize our product candidates;
- our ability to fund future operating expenses, including any future launch of oliceridine, if approved, and capital expenditures with our current cash resources or to secure additional funding in the future;
- our planned nonclinical studies and clinical trials for our product candidates;
- the timing and likelihood of obtaining and maintaining regulatory approvals for our product candidates;
- the extent of clinical trials potentially required by the FDA for our product candidates;
- the clinical utility and market acceptance of our product candidates, particularly in light of existing and future competition;
- our sales, marketing, and manufacturing capabilities and strategy;
- our intellectual property position; and
- our ability to identify additional product candidates with significant commercial potential that are consistent with our commercial objectives.

You should refer to the "Risk Factors" section of this Quarterly Report and our Annual Report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Quarterly Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

PART I

ITEM 1. FINANCIAL STATEMENTS

TREVENA, INC.

Balance Sheets
(*in thousands, except share and per share data*)

	June 30, 2018 (unaudited)	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 24,036	$ 16,557
Marketable securities	39,462	49,543
Alliance revenue receivable	2,250	—
Prepaid expenses and other current assets	1,543	1,393
Total current assets	67,291	67,493
Restricted cash	1,414	1,413
Property and equipment, net	3,613	3,805
Intangible asset, net	10	11
Total assets	$ 72,328	$ 72,722
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 592	$ 1,424
Accrued expenses and other current liabilities	3,651	4,303
Current portion of loans payable, net	12,494	12,425
Deferred revenue	3,000	—
Deferred rent	65	61
Total current liabilities	19,802	18,213
Loans payable, net	10,873	15,725
Capital leases, net of current portion	25	31
Deferred rent, net of current portion	2,926	3,006
Warrant liability	6	10
Other long term liabilities	—	1,104
Total liabilities	33,632	38,089
Commitments and contingencies (Note 6)		
Stockholders' equity:		
Common stock—$0.001 par value; 200,000,000 and 100,000,000 shares authorized June 30, 2018 and December 31, 2017, respectively, 73,507,985 and 62,310,795 shares issued and outstanding at June 30, 2018 and December 31, 2017, respectively	74	62
Preferred stock—$0.001 par value; 5,000,000 shares authorized, none issued or outstanding at June 30, 2018 and December 31, 2017	—	—
Additional paid-in capital	414,457	392,103
Accumulated deficit	(375,815)	(357,490)
Accumulated other comprehensive loss	(20)	(42)
Total stockholders' equity	38,696	34,633
Total liabilities and stockholders' equity	$ 72,328	$ 72,722

See accompanying notes to financial statements.

TREVENA, INC.

Statements of Operations and Comprehensive Loss (Unaudited)
(*in thousands, except share and per share data*)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Revenue:				
Alliance revenue	$ 2,500	$ —	$ 2,500	$ —
Operating expenses:				
General and administrative	5,926	4,385	10,998	9,264
Research and development	5,128	15,499	9,726	31,595
Restructuring charges	41	—	64	—
Total operating expenses	11,095	19,884	20,788	40,859
Loss from operations	(8,595)	(19,884)	(18,288)	(40,859)
Other income (expense):				
Change in fair value of warrant liability	4	19	4	56
Net gain (loss) on asset disposals	(107)	1	116	1
Miscellaneous income	500	—	1,428	628
Interest income	226	163	425	337
Interest expense	(597)	(731)	(1,275)	(1,309)
Gain on foreign currency exchange	10	—	10	—
Total other income (expense)	36	(548)	708	(287)
Loss before income tax expense	(8,559)	(20,432)	(17,580)	(41,146)
Foreign income tax expense	(745)	—	(745)	—
Net loss attributable to common stockholders	$ (9,304)	$ (20,432)	$ (18,325)	$ (41,146)
Other comprehensive gain (loss), net:				
Unrealized gain (loss) on marketable securities	26	(8)	22	(59)
Other comprehensive gain (loss), net:	26	(8)	22	(59)
Comprehensive loss	$ (9,278)	$ (20,440)	$ (18,303)	$ (41,205)
Per share information:				
Net loss per share of common stock, basic and diluted	$ (0.13)	$ (0.35)	$ (0.27)	$ (0.71)
Weighted average common shares outstanding, basic and diluted	69,664,994	58,381,868	67,127,711	57,642,379

See accompanying notes to financial statements.

TREVENA, INC.

Statement of Stockholders' Equity (Unaudited)

For the period from January 1, 2018 to June 30, 2018
(*in thousands, except share data*)

	Stockholders' Equity					
	Common Stock					
	Number of Shares	$0.001 Par Value	Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
Balance, January 1, 2018	62,310,795	$ 62	$ 392,103	$ (357,490)	$ (42)	$ 34,633
Stock-based compensation expense	—	—	2,785	—	—	2,785
Exercise of stock options	132,952	—	83	—	—	83
Issuance of common stock, net of issuance costs	11,064,238	12	19,486	—	—	19,498
Unrealized gain on marketable securities	—	—	—	—	22	22
Net loss	—	—	—	(18,325)	—	(18,325)
Balance, June 30, 2018	73,507,985	$ 74	$ 414,457	$ (375,815)	$ (20)	$ 38,696

See accompanying notes to financial statements.

TREVENA, INC.

Statements of Cash Flows (Unaudited)
(*in thousands*)

	Six Months Ended June 30,	
	2018	**2017**
Operating activities:		
Net loss	$ (18,325)	$ (41,146)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	340	158
Stock-based compensation	2,785	3,687
Noncash interest expense on loans	446	530
Revaluation of warrant liability	(4)	(56)
Amortization (accretion) of bond premium (discount) on marketable securities	(25)	316
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(2,400)	(1,674)
Accounts payable, accrued expenses and other liabilities	(1,560)	(9,563)
Deferred revenue	3,000	—
Net cash used in operating activities	(15,743)	(47,748)
Investing activities:		
Purchases of property and equipment	(147)	(2,019)
Maturities of marketable securities	32,550	48,443
Purchases of marketable securities	(22,422)	(32,646)
Net cash provided by investing activities	9,981	13,778
Financing activities:		
Proceeds from exercise of common stock options	83	355
Proceeds from issuance of common stock, net	19,498	13,687
Capital lease payments	(6)	(3)
Proceeds from loans payable, net	—	9,921
Repayments of loans payable, net	(6,333)	—
Net cash provided by financing activities	13,242	23,960
Net increase (decrease) in cash and cash equivalents	7,480	(10,010)
Cash, cash equivalents and restricted cash—beginning of period	17,970	25,459
Cash, cash equivalents and restricted cash—end of period	$ 25,450	$ 15,449
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 827	$ 778
Fair value of common stock warrants issued	$ —	$ 184

See accompanying notes to financial statements.

TREVENA, INC.

Notes to Unaudited Financial Statements
June 30, 2018

1. Organization and Description of the Business

Trevena, Inc., or the Company, was incorporated in Delaware as Parallax Therapeutics, Inc. on November 9, 2007. The Company began operations in December 2007, and its name was changed to Trevena, Inc. on January 3, 2008. The Company is a biopharmaceutical company developing innovative therapies based on breakthrough science to benefit patients and healthcare providers confronting serious medical conditions. The Company operates in one segment and has its principal office in Chesterbrook, Pennsylvania.

Since commencing operations in 2007, the Company has devoted substantially all of its financial resources and efforts to research and development, including preclinical studies and clinical trials. The Company has never been profitable and has not yet commenced commercial operations. In January 2018, the United States Food and Drug Administration, or FDA, accepted the new drug application, or NDA, submission for oliceridine, the Company's lead product candidate. The FDA also indicated that the Prescription Drug User Fee Act, or PDUFA, review date for the oliceridine NDA is November 2, 2018 and that it plans to hold an advisory committee meeting, likely in October 2018, to discuss the NDA. If oliceridine ultimately receives regulatory approval, the Company plans to commercialize it in the United States, either on its own or with a commercial partner, for use in acute care settings such as hospitals and ambulatory surgery centers; outside the United States, the Company plans to commercialize oliceridine in certain countries with commercial partners and, in the second quarter of 2018, the Company announced license agreements with partners in South Korea and China. See Notes 7 and 8 for additional information.

Since the Company’s inception, the Company has incurred losses and negative cash flows from operations. At June 30, 2018, the Company had an accumulated deficit of $375.8 million. The Company’s net loss was $18.3 million and $41.1 million for the six months ended June 30, 2018 and 2017, respectively. The Company expects its cash and cash equivalents of $24.0 million and marketable securities of $39.5 million as of June 30, 2018, together with interest thereon, as well as proceeds from the sale of shares of common stock under the Company’s at the market, or ATM, sales agreement with Cowen and Company, LLC, or Cowen, and from the receipt of $2.3 million related to an upfront payment from ex-U.S. licensing activities in China between June 30, 2018 and the date of this filing, to be sufficient to fund its operating expenses and capital expenditure requirements for at least twelve months following the date of this filing. If approved by FDA on November 2, 2018, and following Drug Enforcement Administration, or DEA, Scheduling, the Company expects to launch oliceridine in the United States in the first half of 2019. The extent of the Company’s commercial efforts for oliceridine, including the number of sales representatives and medical science liaisons at launch, will depend to a significant extent on the success of the Company’s fundraising efforts between the date of this filing and the launch date.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America, or GAAP. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification, or ASC, and Accounting Standards Update, or ASU, of the Financial Accounting Standards Board, or FASB. The Company’s functional currency is the U.S. dollar.

The financial statements include all normal and recurring adjustments that are considered necessary for the fair presentation of the Company’s balance sheet as of June 30, 2018, its results of operations and its comprehensive loss for the three and six months ended June 30, 2018 and 2017, its statement of stockholders’ equity for the period from January 1, 2018 to June 30, 2018, and its cash flows for the six months ended June 30, 2018 and 2017. The information included in this Quarterly Report on Form 10-Q should be read in conjunction with the financial statements and accompanying notes included in the Company’s most recent Annual Report on Form 10-K for the year ended December 31, 2017. Since the date of those financial statements, there have been no changes to the Company’s significant accounting policies. The financial data and other information disclosed in these notes related to the six

months ended June 30, 2018 and 2017 are not necessarily indicative of the results to be expected for the year ending December 31, 2018, any other interim periods, or any future year or period.

Revenue

In accordance with FASB's ASC 606, *Revenue from Contracts with Customers*, or ASC 606, the Company 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 revenue recognition for arrangements that the Company determines are within the scope of ASC 606, it performs the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

The Company applies the five-step model to contracts when it determines that it is probable it will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC Topic 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Amounts received prior to satisfying the revenue recognition criteria are recognized as deferred revenue in the Company's balance sheet. Amounts expected to be recognized as revenue within the twelve months following the balance sheet date are classified as Current portion of deferred revenue. Amounts not expected to be recognized as revenue within the twelve months following the balance sheet date are classified as Deferred revenue, net of current portion.

Alliance Revenues

The Company's revenues have primarily been generated through licensing arrangements. The terms of these agreements typically include payment to the Company of one or more of the following: nonrefundable, up-front license fees; regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized as it fulfills its obligations under each of its agreements, the Company performs the following steps:

(i) identification of the promised goods or services in the contract;

(ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract;

(iii) measurement of the transaction price, including the constraint on variable consideration;

(iv) allocation of the transaction price to the performance obligations; and

(v) recognition of revenue when (or as) the Company satisfies each performance obligation.

See Note 8 for additional details surrounding the Company's licensing arrangements.

The Company also assesses whether there is an option in a contract to acquire additional goods or services. An option gives rise to a performance obligation only if the option provides a material right to the customer that it would not receive without entering into that contract. Factors that the Company considers in evaluating whether an option represents a material right include, but are not limited to: (i) the overall objective of the arrangement, (ii) the benefit the collaborator might obtain from the arrangement without exercising the option, (iii) the cost to exercise the option (e.g. priced at a significant and incremental discount) and (iv) the likelihood that the option will be exercised. With respect to options determined to be performance obligations, the Company recognizes revenue when those future goods or services are transferred or when the options expire.

The Company's revenue arrangements may include the following:

Up-front License Fees: If a license is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from nonrefundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone Payments: At the inception of an agreement that includes regulatory or commercial milestone payments, the Company evaluates whether each milestone is considered probable of being achieved 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 control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received.At each reporting period, the Company assesses the probability of achievement of each milestone under its current agreements.

Research and Development Activities: Under the Company's current collaboration and license arrangements, if the Company is entitled to reimbursement for costs for services provided by the Company, it expects such reimbursement would be an offset to research and development expenses.

Royalties: If the Company is entitled to receive sales-based royalties from its collaborator, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, provided the reported sales are reliably measurable, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Manufacturing Supply and Research Services: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. The Company assesses if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations.

The Company receives payments from its licensees based on schedules established in each contract. Upfront payments are recorded as deferred revenue upon receipt, and may require deferral of revenue recognition to a future period until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Income Taxes

In accordance with ASC 270, *Interim Reporting*, and ASC 740, *Income Taxes*, the Company is required at the end of each interim period to determine the best estimate of its annual effective tax rate and then apply that rate in providing for income taxes on a current year-to-date (interim period) basis. For the six months ended June 30, 2018, the Company recorded foreign income tax expense related to withholdings associated with our ex-U.S. licensing activities. For the six months ended June 30, 2017, the Company recorded no tax expense or benefit due to the expected

2017 loss and its historical losses. The Company has not recorded its net deferred tax asset as of either June 30, 2018 or December 31, 2017 because it maintained a full valuation allowance against all deferred tax assets as of these dates as management has determined that it is not more likely than not that the Company will realize these future tax benefits. As of June 30, 2018 and December 31, 2017, the Company had no uncertain tax positions.

In December 2017, the Tax Cuts and Jobs Act, or TCJA, was signed into law. Among other things, the TCJA permanently lowers the corporate federal income tax rate to 21% from the existing maximum rate of 35%, effective for tax years including or commencing January 1, 2018. As a result of the reduction of the corporate federal income tax rate to 21%, GAAP requires companies to revalue their deferred tax assets and deferred tax liabilities as of the date of enactment, with the resulting tax effects accounted for in the reporting period of enactment. This revaluation resulted in a provision of $27.6 million to income tax expense in and a corresponding reduction in the valuation allowance in the fourth quarter of 2017. As a result, there was no impact to the Company's statement of operations and comprehensive loss as a result of reduction in tax rates. The Company's preliminary estimate of the TCJA and the remeasurement of its deferred tax assets and liabilities is subject to the finalization of management's analysis related to certain matters, such as developing interpretations of the provisions of the TCJA, changes to certain estimates and the filing of the Company's tax returns. U.S. Treasury regulations, administrative interpretations or court decisions interpreting the TCJA may require further adjustments and changes in the Company's estimates. The final determination of the TCJA and the remeasurement of the Company's deferred assets and liabilities will be completed as additional information becomes available, but no later than one year from the enactment of the TCJA.

Recently Adopted Accounting Standards

In December 2017, the SEC staff issued Staff Accounting Bulletin No. 118, or SAB 118, which provides guidance on accounting for the tax effects of the TCJA. SAB 118 was issued to address the application of GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Act and allows the Company to record provisional amounts during a measurement period not to extend beyond one year of the TCJA enactment date. The Company was able to reasonably estimate certain effects of the TCJA as of December 31, 2017 and has not changed the preliminary estimates as of June 30, 2018.

In May 2017, the FASB issued ASU No. 2017-09,*Stock Compensation - Scope of Modification Accounting,*which amends the scope of modification accounting for share-based payment arrangements. The amendment provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting. The new standard is effective for fiscal years beginning after December 15, 2017. The adoption of this standard did not have an impact on the Company's consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15,*Statement of Cash Flows (Topic 230),* to clarify how certain cash receipts and payments should be presented in the statement of cash flows. The standard is effective for annual periods beginning after December 15, 2017 and interim periods within that reporting period. The adoption of this standard did not have an impact on the Company's consolidated financial statements.

In May 2014, the FASB issued ASU 2014-09,*Revenue from Contracts with Customers.* ASU 2014-09 is a comprehensive new revenue recognition model requiring a company to recognize revenue to depict the transfer of goods or services to a customer in an amount reflecting the consideration it expects to receive in exchange for those goods or services. Additionally, in March 2016, the FASB issued ASU 2016-08, *Revenue from Contracts with Customers, Principal versus Agent Considerations* ASU 2016-08 amends the principal versus agent guidance in ASU 2014-09 to clarify how an entity should identify the unit of accounting for the principal versus agent evaluation and how it should apply the control principal to certain types of arrangements. The effective date for both standards is January 1, 2018. The Company adopted these standards on January 1, 2018 and elected the modified retrospective transition method, meaning the cumulative effect of applying the new guidance, if any, was recognized at that date as an adjustment to the opening accumulated deficit balance. There was no impact to the Company's financial statements upon adoption, as the Company did not have any contracts with customers prior to, or, as of the adoption date.

Recent Accounting Standards Not Yet Adopted

In February 2018, the FASB issued ASU 2018-02,*Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*, which provides the option to reclassify stranded tax effects within accumulated other

comprehensive income to retained earnings. This option would be available in each period in which the effect of the change in the U.S. federal corporate income tax rate in the Tax Cuts and Jobs Act (or a portion thereof) is recorded. This is effective for the Company beginning after December 15, 2018, with early adoption permitted. These amendments should be applied in the period of adoption or retrospectively to each period in which the effect of the change in the U.S federal corporate income tax rate in the Tax Cuts and Jobs Act is recognized. The Company is evaluating the effect this standard will have on its financial statements and related disclosures.

In February 2016, the FASB issued ASU 2016-02,*Leases (Topic 842*), which requires lessees to record most leases on their balance sheets and disclose key information about leasing arrangements in an effort to increase transparency and comparability among organizations. The standard is effective for annual periods beginning after December 15, 2018 and interim periods within that reporting period. Early adoption is permitted. The Company is evaluating the effect this standard will have on its financial statements and related disclosures.

3. Fair Value of Financial Instruments

ASC Topic 820, *Fair Value Measurement,* establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances.

ASC 820 identifies fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tier fair value hierarchy that distinguishes among the following:

- Level 1-Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access.

- Level 2-Valuations based on quoted prices for similar assets or liabilities in active markets, quoted prices for identical or similar assets or liabilities in markets that are not active and models for which all significant inputs are observable, either directly or indirectly.

- Level 3-Valuations based on inputs that are unobservable and significant to the overall fair value measurement.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Cash, Cash Equivalents and Marketable Securities

The following table presents fair value of the Company's cash, cash equivalents, and marketable securities as of June 30, 2018 and December 31, 2017 (in thousands):

	June 30, 2018						
	Adjusted Cost	Unrealized Gains	Unrealized Loss	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 8,704	$ —	$ —	$ 8,704	$ 7,290	$ 1,414	$ —
Level 1 (1):							
Money market funds	16,746	—	—	16,746	16,746	—	—
U.S. treasury securities	4,983	—	(1)	4,982	—	—	4,982
Subtotal	21,729	—	(1)	21,728	16,746	—	4,982
Level 2 (2):							
U.S. government agency securities	34,499	—	(19)	34,480	—	—	34,480
Total	$ 64,932	$ —	$ (20)	$ 64,912	$ 24,036	$ 1,414	$ 39,462

	December 31, 2017						
	Adjusted Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 6,783	$ —	$ —	$ 6,783	$ 5,370	$ 1,413	$ —
Level 1 (1):							
Money market funds	11,187	—	—	11,187	11,187	—	—
U.S. treasury securities	1,991	—	—	1,991	—	—	1,991
Subtotal	13,178	—	—	13,178	11,187	—	1,991
Level 2 (2):							
U.S. government agency securities	47,594	—	(42)	47,552	—	—	47,552
Total	$ 67,555	$ —	$ (42)	$ 67,513	$ 16,557	$ 1,413	$ 49,543

(1) The fair value of Level 1 securities is estimated based on quoted prices in active markets for identical assets or liabilities.

(2) The fair value of Level 2 securities is estimated based on observable inputs other than quoted prices in active markets for identical assets and liabilities, quoted prices for identical or similar assets or liabilities in inactive markets, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

The Company classifies investments available to fund current operations as current assets on its balance sheets. As of June 30, 2018, the Company did not hold any investment securities exceeding a one-year maturity.

Unrealized gains and losses on marketable securities are recorded as a separate component of accumulated other comprehensive income (loss) included in stockholders' equity. Realized gains (losses) are included in interest income (expense) in the statement of operations and comprehensive income (loss) on a specific identification basis. The Company did not record any realized gains or losses during the three and six months ended June 30, 2018 and 2017. To date, the Company has not recorded any impairment charges on marketable securities related to other-than-temporary declines in market value.

The Company recognizes transfers between levels of the fair value hierarchy as of the end of the reporting period. There were no transfers between Level 2 and Level 3 during the six months ended June 30, 2018 or the year ended December 31, 2017.

4. Loans Payable

In September 2014, the Company entered into a loan and security agreement with Oxford Finance LLC and Pacific Western Bank (formerly Square 1Bank) (together, the lenders), pursuant to which the lenders agreed to lend the Company up to $35.0 million in a three-tranche series of term loans (Term Loans A, B, and C). Upon initially entering into the agreement, the Company borrowed $2.0 million under Term Loan A. In April 2015, the Company amended the agreement with the lenders to change the draw period for Term Loan B. In December 2015, the Company further amended the agreement with the lenders to, among other things, change the draw period for Term Loan C, modify the interest only period, and modify the maturity date of the loan. In December 2015, the Company borrowed the Term Loan B tranche of $16.5 million. The Company's ability to draw an additional $16.5 million under Term Loan C was subject to the satisfaction of one or more specified triggers related to the results of the Company's Phase 2b clinical trial of TRV027, which were announced in May 2016. Although those triggers were not attained, in December 2016, the Company and the lenders modified the terms and conditions under which the Company could exercise an option to draw $10.0 million of Term Loan C. In March 2017, the Company borrowed the Term Loan C tranche of $10.0 million.

Borrowings under Term Loans A and B accrue interest at a fixed rate of 6.50% per annum. Borrowings under Term Loan C accrue interest at a fixed rate of 6.98% per annum. The Company was required to make payments of interest only on borrowings under the loan agreement on a monthly basis through and including January 1, 2018. Payments of principal in equal monthly installments and accrued interest began January 1, 2018 and will continue to be due until the loan matures on March 1, 2020. Upon the last payment date of the amounts borrowed under the agreement, the Company will be required to pay a final payment fee equal to 6.6% of the aggregate amounts borrowed, which is recorded as interest expense over the term of the loans payable. In addition, if the Company repays Term Loan A, Term Loan B, or Term Loan C prior to the applicable maturity date, it will pay the lenders a prepayment fee of 1.0% of each of Term Loans A and B, and 2.0% of Term Loan C, if the prepayment occurs on or between April 1, 2018 and March 31, 2019, and 1.0% of Term Loan C, if the prepayment occurs on or after April 1, 2019.

The Company's obligations under the loan and security agreement are secured by a first priority security interest in substantially all of the assets of the Company, including the Company's cash, cash equivalents, and marketable securities but excluding the Company's intellectual property (together, the collateral). The Company has agreed not to pledge or otherwise encumber its intellectual property, other than through grants of certain permitted non-exclusive or exclusive licenses or other conveyances of its intellectual property.

The loan and security agreement includes affirmative and restrictive covenants, including: (a) financial reporting requirements; (b) limitations on the incurrence of indebtedness; (c) limitations on liens; (d) limitations on certain merger and acquisition transactions; (e) limitations on dispositions of certain assets; (f) limitations on fundamental corporate changes (including changes in control); (g) limitations on investments; (h) limitations on payments and distributions and (i) other covenants. The agreement also contains certain events of default, including for payment defaults, breaches of covenants, a material adverse change in the Company's business, operations or condition (financial or otherwise), a material impairment in the value of the collateral or in the prospect of repayment of the Company's obligations to the lender, certain levies, attachments and other restraints on the Company's business, insolvency, defaults under other agreements and misrepresentations. Upon an event of default, the lenders have the right to foreclose upon the available collateral, including the Company's existing cash and cash equivalents and marketable securities.

In connection with entering into the agreement, the Company issued to the lenders and the placement agent warrants to purchase an aggregate of 7,678 shares of Trevena's common stock, of which 5,728 shares remain outstanding as of June 30, 2018. These detachable warrant instruments have qualified for equity classification and have been allocated upon the relative fair value of the base instrument and the warrants, according to the guidance of ASC 470-20-25-2. These warrants are exercisable immediately and have an exercise price of $5.8610 per share. The warrants may be exercised on a cashless basis and will terminate on the earlier of September 19, 2024 or the closing of a merger or consolidation transaction in which the Company is not the surviving entity. In connection with the draw of Term Loan B, the Company issued to the lenders and the placement agent additional warrants to purchase an aggregate of 34,961 shares of Trevena common stock, all of which remain outstanding at June 30, 2018. These warrants have substantially the same terms as those noted above, have an exercise price of $10.6190 per share and an expiration date of December 23, 2025. In connection with draw of Term Loan C, the Company issued to the lenders and placement agent additional warrants to purchase an aggregate of 62,241 shares of the Company's common stock, all of which remain

outstanding at June 30, 2018. These warrants have substantially the same terms as those noted above, and have an exercise price of $3.6150 per share and an expiration date of March 31, 2027.

As of June 30, 2018, borrowings of $22.2 million attributable to Term Loans A, B, and C remain outstanding. Interest expense of $0.8 million and $0.8 million was recorded during the six months ended June 30, 2018 and 2017, respectively. The Company incurred lender and third party costs of $1.0 million related to the issuance of its term loans. Per ASU 2015-3, *Interest-Imputation of Interest*, debt discount and debt issuance costs are to be presented as a contra-liability to the debt on the balance sheet. These costs will be amortized to interest expense over the life of the loans using the effective interest method. Immaterial amounts of debt discount and debt issuance cost were amortized to interest expense during the three and six months ended June 30, 2018 and 2017, respectively.

The following table summarizes how the issuance of Term Loans A, B, and C are reflected on the balance sheet at June 30, 2018 and December 31, 2017 (in thousands):

	June 30, 2018	December 31, 2017
Gross proceeds	$ 22,167	$ 28,500
Debt discount and debt issuance costs	1,200	(350)
Carrying value	23,367	28,150
Current portion of loans payable, net	12,494	12,425
Loans payable, net	$ 10,873	$ 15,725

The accretion of the final fee payment is presented as part of Debt discount and debt issuance costs, a component of loans payable, as of June 30, 2018 and as other long term liabilities as of December 31, 2017.

5. Stockholders' Equity

Equity Offerings

On December 14, 2015, the Company entered into an ATM sales agreement with Cowen, or the Prior ATM Agreement, to offer and sell, from time to time at the Company's sole discretion, shares of its common stock, having an aggregate offering price of up to $75.0 million through Cowen as its sales agent. Sales under the Prior ATM Agreement are deemed to be "at the market offerings", as defined in Rule 415 under the Securities Act of 1933, as amended, or the Securities Act. Under the Prior ATM Agreement, the Company was required to pay Cowen a commission of up to three percent of the gross sales proceeds and provided Cowen with customary indemnification rights. In the six months ended June 30, 2018, the Company issued and sold 11,064,238 shares of common stock under the Prior ATM Agreement at a weighted average price per share of $1.81. The net offering proceeds to the Company were approximately $19.5 million after deducting related expenses, including commissions. The Prior ATM Agreement terminated on June 29, 2018 when the Company's Registration Statement on Form S-3 (File No. 333-225685) was declared effective by the SEC. Accordingly, as of June 30, 2018, there was no remaining capacity available under this ATM facility.

On June 15, 2018, the Company entered into a new ATM sales agreement with Cowen to offer and sell, from time to time at the Company's sole discretion, shares of its common stock, having an aggregate offering price of up to $50.0 million through Cowen as its sales agent. Sales of the shares are deemed to be "at the market offerings", as defined in Rule 415 under the Securities Act. The Company is required to pay Cowen a commission of up to three percent of the gross sales proceeds and has provided Cowen with customary indemnification rights. During the second quarter of 2018, no sales were made under this ATM facility and the entire $50 million capacity remained available as of June 30, 2018.

Equity Incentive Plans

The Company utilizes equity incentive plans to grant various forms of stock options and restricted stock to eligible employees, directors and consultants to the Company. Under all of such plans, the amount, terms of grants and exercisability provisions are determined by the board of directors or its designee. The term of the options may be up to 10 years, and options are exercisable in cash or as otherwise determined by the board of directors. Vesting generally occurs over a period of not greater than 4 years. For performance-based stock awards, we recognize expense when achievement of the performance factor is probable, over the requisite service period.

The estimated grant-date fair value of the Company's stock-based awards is amortized ratably over the awards' service periods. Stock-based compensation expense recognized was as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Research and development	$ 386	$ 735	$ 744	$ 1,441
General and administrative	901	1,158	2,041	2,246
Total stock-based compensation	$ 1,287	$ 1,893	$ 2,785	$ 3,687

	Options Outstanding		
	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
Balance, December 31, 2017	8,624,223	$ 5.22	7.17
Granted	3,085,125	1.79	
Exercised	(132,952)	0.63	
Forfeited/Cancelled	(2,190,948)	4.31	
Balance, June 30, 2018	9,385,448	$ 4.37	7.35
Vested or expected to vest at June 30, 2018	9,385,448	$ 4.37	7.35
Exercisable at June 30, 2018	4,225,244	$ 5.46	5.25

The intrinsic value of the options exercisable as of June 30, 2018 was $0.2 million, based on the Company's closing stock price of $1.44 per share and a weighted average exercise price of $5.46 per share. At June 30, 2018, there was $9.8 million of total unrecognized compensation expense related to unvested options that will be recognized over the weighted average remaining period of 2.25 years.

The Company uses the Black-Scholes option pricing model to estimate the fair value of stock options at the grant date. The Black-Scholes model requires the Company to make certain estimates and assumptions, including estimating the fair value of the Company's common stock, assumptions related to the expected price volatility of the Company's stock, the period during which the options will be outstanding, the rate of return on risk-free investments and the expected dividend yield for the Company's common stock.

The per-share weighted-average grant date fair value of the options granted to employees and directors during the six months ended June 30, 2018 and 2017 was estimated at $1.19 and $3.20 per share, respectively, on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Six Months Ended June 30,	
	2018	2017
Expected term of options (in years)	5.8	6.2
Risk-free interest rate	2.7 %	2.1 %
Expected volatility	74.9 %	75.7 %
Dividend yield	0 %	0 %

Shares Available for Future Grant

At June 30, 2018, the Company has the following shares available to be granted under its equity incentive plans:

	2013 Plan	Inducement Plan
Available at December 31, 2017	991,613	293,000
Authorized	2,492,431	—
Granted	(2,763,125)	(322,000)
Forfeited/Cancelled	2,074,823	116,125
Available at June 30, 2018	2,795,742	87,125

Shares Reserved for Future Issuance

At June 30, 2018, the Company has reserved the following shares of common stock for issuance:

Stock options outstanding under 2013 Plan	8,972,573
Shares available for future grant under 2013 Plan	2,795,742
Stock options outstanding under Inducement Plan	412,875
Shares available for future grant under Inducement Plan	87,125
Employee stock purchase plan	225,806
Warrants outstanding	123,091
Total shares of common stock reserved for future issuance	12,617,212

6. Commitments and Contingencies

Legal Proceedings

The Company is not involved in any legal proceeding that it expects to have a material effect on its business, financial condition, results of operations and cash flows.

7. Licensing Arrangements

License and Commercialization Agreement with Pharmbio Korea Inc.

In April 2018, the Company entered into an exclusive license agreement with Pharmbio Korea Inc., or Pharmbio, for the development and commercialization of oliceridine for the management of moderate to severe acute pain in South Korea. Under the terms of the agreement, the Company received an upfront, non-refundable cash payment of $3.0 million in connection with execution of the agreement, a cash commercial milestone of up to $0.5 million if oliceridine is approved in South Korea and tiered royalties on product sales in South Korea ranging from high single digits to 20%, less applicable withholding taxes. As part of the agreement, Trevena also granted Pharmbio an option to manufacture oliceridine, on a non-exclusive basis, for the development and commercialization of the product in South Korea, subject to a separate arrangement to be entered into if Pharmbio exercises the option.

In accordance with the terms of the agreement, Pharmbio is solely responsible for all development and regulatory activities in South Korea. The parties have formed a Joint Development Committee with equal representation from the Company and Pharmbio to provide overall coordination and oversight of the development of oliceridine in

South Korea. The parties also agreed to form a Joint Manufacturing and Commercialization Committee at least six months prior to the anticipated date of regulatory approval of oliceridine in South Korea to provide overall coordination and oversight of the manufacture and commercialization of oliceridine in South Korea.

See Note 8 for accounting analysis under ASC 606.

License Agreement with Jiangsu Nhwa Pharmaceutical Co. Ltd.

In April 2018, the Company also entered into an exclusive license agreement with Jiangsu Nhwa Pharmaceutical Co. Ltd., or Nhwa, for the development and commercialization of oliceridine for the management of moderate to severe acute pain in China. Under this agreement, the Company will receive an upfront, non-refundable cash payment of $2.5 million (less applicable withholding taxes of $0.3 million) and is eligible to receive cash milestone payments of $3.0 million upon regulatory approval of oliceridine in each of the United States and China, up to an additional $6.0 million of commercialization milestones based on product sales levels in China, and a ten percent royalty on all net product sales in China, less applicable withholding taxes. As part of the agreement, Trevena also granted Nhwa an option to manufacture oliceridine, on an exclusive basis in China, for the development and commercialization of the product in China. As of June 30, 2018, Nhwa has elected to exercise this manufacturing option and a separate agreement will be entered into. The Company received the upfront cash payment, net of withholdings, in July 2018.

In accordance with the terms of the agreement, Nhwa is solely responsible for all development and regulatory activities in China. The parties have formed a Joint Development Committee with equal representation from the Company and Nhwa to provide overall coordination and oversight of the development of oliceridine in China. The parties also agreed to form a Joint Manufacturing and Commercialization Committee at least six months prior to the anticipated date of regulatory approval of oliceridine in China to provide overall coordination and oversight of the manufacture and commercialization of oliceridine in China.

See Note 8 for accounting analysis under ASC 606.

8. Revenue

The Company accounts for revenue under FASB's ASC 606, *Revenue from Contracts with Customers*, or ASC 606, under which revenue is recognized when, or as, performance obligations under the terms of a contract are satisfied, which occurs when control of the promised products or services is transferred to customers.

Alliance Revenue

Alliance revenue for the three months ended June 30, 2018 represents revenue from contracts with customers in licensing arrangements accounted for in accordance with ASC Topic 606, which the Company adopted in the first quarter of 2018, as more fully described in Note 2 and Note 7. There was no previously recorded Alliance revenue.

For the three and six months ended June 30, 2018, Alliance revenue in the accompanying statements of operations and comprehensive loss is comprised of the following:

	Three Months Ended June 30, 2018	Six Months Ended June 30, 2018
Pharmbio Korea Inc.	$ —	$ —
Jiangsu Nhwa Pharmaceutical Co. Ltd.	2,500	2,500
	$ 2,500	$ 2,500

There was no Alliance revenue activity in 2017. The 2018 Alliance revenue recognized relates to the upfront payments received from Nhwa once the related performance obligation was satisfied. This performance obligation was satisfied once the Company had transferred the license and know-how to Nhwa and Nhwa could begin to benefit from this transfer. The revenue related to the Pharmbio agreement has been deferred, based on the date at which the license

and know-how was transferred, and will be recognized in the third quarter of 2018, at the time the Company completed its performance obligation. The Company determined that participation in the Joint Development Committees and Joint Manufacturing and Commercialization Committees were deemed immaterial in the context of the contract.

The income tax expense resulting from these transactions represents foreign withholding taxes as a result of alliance revenue from the contracts. As the Company has incurred losses in recent years, no material U.S. federal, state, or foreign income taxes have been accrued.

9. Net Loss Per Common Share

The following table sets forth the computation of basic and diluted net loss per share for the periods indicated (in thousands, except share and per share data):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Basic and diluted net loss per common share calculation:				
Net loss	$ (9,304)	$ (20,432)	$ (18,325)	$ (41,146)
Net loss attributable to common stockholders	$ (9,304)	$ (20,432)	$ (18,325)	$ (41,146)
Weighted average common shares outstanding	69,664,994	58,381,868	67,127,711	57,642,379
Net loss per share of common stock - basic and diluted	$ (0.13)	$ (0.35)	$ (0.27)	$ (0.71)

The following outstanding securities at June 30, 2018 and 2017 have been excluded from the computation of diluted weighted shares outstanding, as they would have been anti-dilutive:

	June 30,	
	2018	2017
Options outstanding	9,385,448	8,520,152
Warrants	123,091	123,091
Total	9,508,539	8,643,243

10. Other Comprehensive Loss

The following table presents changes in the components of accumulated other comprehensive loss (in thousands):

Balance, December 31, 2017	$ (42)
Net unrealized gain on marketable securities	22
Balance, June 30, 2018	$ (20)

There were no reclassifications out of accumulated other comprehensive loss during the six months ended June 30, 2018 and 2017. There was no tax effect during the three six and months ended June 30, 2018 and 2017.

11. Restructuring Charges

On October 11, 2017, upon the approval of the Company's Board of Directors, the Company announced a restructuring and reduction in force of approximately 30% of the Company's workforce, or 21 employees. As part of this restructuring, the Company also halted its investment in early stage research. The Company incurred pre-tax restructuring charges of $1.8 million during the year ended December 31, 2017, primarily related to severance and personnel related costs in addition to lease termination payments. As of December 31, 2017, the Company’s restructuring liability totaled $1.1 million. During the three and six months ended June 30, 2018, the Company made severance payments totaling $0.2 million and $0.9 million, respectively. As of June 30, 2018, the Company’s restructuring liability totals $0.2 million, which has been recorded within accrued expenses on the Company’s balance sheet.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and result of operations should be read in conjunction with our unaudited financial statement and related notes that appear in Item 1 of this Quarterly Report on Form 10-Q and with our audited financial statements and related notes for the year ended December 31, 2017, which are included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC, on March 7, 2018. Unless the context otherwise requires, we use the terms "Trevena," "company," "we," "us" and "our" to refer to Trevena, Inc.

Overview

Using our proprietary product platform, we have identified and are developing the following product candidates:

- Oliceridine injection: We are developing oliceridine, a G protein biased ligand of the μ opioid receptor, for the management of moderate-to-severe acute pain where intravenous, or IV, administration is preferred. In February 2017, we announced positive top-line results from our Phase 3 APOLLO-1 and APOLLO-2 pivotal efficacy studies of oliceridine in moderate-to-severe acute pain following bunionectomy and abdominoplasty, respectively. In both studies, all dose regimens achieved their primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate. In July 2017, we announced that we had completed enrollment in the Phase 3 open-label ATHENA safety study to support the new drug application, or NDA, for oliceridine. In the study, 768 patients were administered oliceridine to manage pain associated with a wide range of procedures and diagnoses. In January 2018, we announced that the United States Food and Drug Administration, or FDA, had accepted the NDA we submitted for oliceridine. The FDA also indicated that the Prescription Drug User Fee Act, or PDUFA, review date for the oliceridine NDA is November 2, 2018 and that it plans to hold an advisory committee meeting, likely in October 2018, to discuss the NDA. If oliceridine ultimately receives regulatory approval, we plan to commercialize it in the United States, either on our own or with a commercial partner, for use in acute care settings such as hospitals and ambulatory surgery centers; outside the United States, we plan to commercialize oliceridine in certain countries with a commercial partner and, in the second quarter of 2018, we announced license agreements with partners in South Korea and China. If approved by FDA on November 2, 2018, and following DEA scheduling, we expect to launch oliceridine in the United States in the first half of 2019.

- TRV250: We are developing TRV250, a G protein biased ligand targeting the δ-receptor, as a compound with a potential first-in-class, non-narcotic mechanism for the treatment of acute migraine. TRV250 also may have utility in a range of other central nervous system, or CNS, indications. Because TRV250 selectively targets the δ-receptor, we believe it will not have the addiction liability of conventional opioids or other μ-opioid related adverse effects like those seen with morphine or oxycodone. In June 2018, we announced the successful completion of our first-time-in-human Phase 1 study of TRV250. Data from this healthy volunteer study showed safety, tolerability, and pharmacokinetics supporting the advancement of TRV250 to Phase 2 proof of concept evaluation in patients, subject to available funds.

We also have identified and have completed the initial Phase 1 studies for TRV734, an orally administered new chemical entity expected to be used for first-line treatment of moderate-to-severe acute and chronic pain. In August 2018, we announced that we are supporting efforts by the National Institute on Drug Abuse to evaluate TRV734 as a potential maintenance treatment for opioid dependence. We intend to continue to focus our efforts for TRV734 on securing a development and commercialization partner for this asset. We also are evaluating a set of novel S1P modulators that may offer a new, non-narcotic approach to managing chronic pain. We expect to complete characterization of the lead compounds in 2018 to determine if any merit IND-enabling studies to support Phase 1 clinical trials.

On April 5, 2018, we announced that Maxine Gowen, Ph.D., Trevena's President and Chief Executive Officer, will retire on October 1, 2018. The Board of Directors has selected Carrie L. Bourdow, who currently serves as

Trevena's Executive Vice President and Chief Operating Officer, to be the Company's next President and Chief Executive Officer, effective October 1, 2018. Dr. Gowen will continue to serve on the Trevena Board of Directors following the date of her resignation.

Since our incorporation in late 2007, our operations have included organizing and staffing our company, business planning, raising capital, and discovering and developing our product candidates. We have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. As of June 30, 2018, we had an accumulated deficit of $375.8 million. Our net loss was $18.3 million and $41.1 million for the six months ended June 30, 2018 and 2017, respectively. Our ability to become and remain profitable depends on our ability to generate revenue or sales. We do not expect to generate significant revenue or sales unless and until we or a collaborator obtain marketing approval for and commercialize oliceridine, TRV250 or TRV734.

In September 2014, we announced we had entered into a senior secured tranched term loan credit facility with Oxford Finance LLC and Pacific Western Bank (formerly Square 1 Bank), of which $22.2 million remains outstanding as of June 30, 2018. As of January 1, 2018, we began making monthly payments of both principal and interest, which will be required until the loan maturity of March 1, 2020.

We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, seek regulatory approval for, and prepare for commercialization of our product candidates and repay our outstanding loan obligations. If we obtain regulatory approval for oliceridine, we expect to incur significant expenses associated with the launch of this product. We will need to obtain substantial additional funding in connection with our continuing operations. We will seek to fund our operations through the sale of equity, debt financings or other sources, including potential collaborations. However, we may be unable to raise additional funds or enter into such other agreements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue our operations, development programs, and/or any future commercialization efforts.

Senior Secured Tranched Term Loan Credit Facility

In September 2014, we entered into a loan and security agreement with Oxford Finance LLC and Pacific Western Bank, or the lenders, pursuant to which they agreed to lend us up to $35 million in a three-tranche series of term loans (Term Loans A, B, and C). Upon initially entering into the agreement, we borrowed $2 million under Term Loan A. On April 13, 2015, we amended the agreement with the lenders to change the draw period for Term Loan B. On December 23, 2015, we further amended the agreement with the lenders to, among other things, change the draw period for Term Loan C, modify the interest only period, and modify the maturity date of the loan. In December 2015, we borrowed the Term Loan B tranche of $16.5 million. Our ability to draw an additional $16.5 million under Term Loan C was subject to the satisfaction of one or more specified triggers related to the results of our Phase 2b clinical trial of TRV027. Although those triggers were not attained, in December 2016, we and the lenders modified the terms and conditions under which we could exercise an option to draw $10 million of Term Loan C. In March 2017, we borrowed the Term Loan C tranche of $10.0 million.

Borrowings under Terms Loans A and B accrue interest at a fixed rate of 6.50% per annum. Borrowings under Term Loan C accrue interest at a fixed rate of 6.98% per annum. We were required to make payments of interest only on borrowings under the loan agreement on a monthly basis through and including January 1, 2018; payments of principal in equal monthly installments and accrued interest began on January 1, 2018 and will continue until the loan matures on March 1, 2020. Upon the last payment date of the amounts borrowed under the agreement, we will be required to pay a final payment fee equal to 6.6% of the aggregate amounts borrowed. In addition, if we repay Term Loan A, Term Loan B, or Term Loan C prior to the applicable maturity date, we will pay the lenders a prepayment fee of 1.0% of each of Term Loans A and B, and 2.0% of Term Loan C, if the prepayment occurs on or between April 1, 2018 and March 31, 2019, and 1.0% of Term Loan C, if the prepayment occurs on or after April 1, 2019.

Our obligations are secured by a first priority security interest in substantially all of our assets, including our cash and cash equivalents and marketable securities, but excluding our intellectual property (together, the collateral). In addition, we have agreed not to pledge or otherwise encumber our intellectual property, with specified exceptions. Upon an event of default, the lenders have the right to foreclose upon the available collateral, including our existing cash and cash equivalents and marketable securities.

In connection with entering into the original agreement, we issued to the lenders and placement agent warrants to purchase an aggregate of 7,678 shares of our common stock, of which 5,728 shares remain outstanding as of June 30, 2018. These warrants are exercisable immediately and have an exercise price of $5.8610 per share. The warrants may be exercised on a cashless basis and will terminate on the earlier of September 19, 2024 or the closing of a merger or consolidation transaction in which we are not the surviving entity. In connection with the draw of Term Loan B, we issued to the lenders and placement agent additional warrants to purchase an aggregate of 34,961 shares of our common stock, all of which remain outstanding as of June 30, 2018. These warrants have substantially the same terms as those noted above, and have an exercise price of $10.6190 per share and an expiration date of December 23, 2025. In connection with the draw of Term Loan C, we issued to the lenders and placement agent additional warrants to purchase an aggregate of 62,241 shares of our common stock, all of which remain outstanding as of June 30, 2018. These warrants have substantially the same terms as those noted above, and have an exercise price of $3.6150 per share and an expiration date of March 31, 2027. These detachable warrant instruments have qualified for equity classification and have been allocated upon the relative fair value of the base instrument and the warrants, according to the guidance of ASC 470-20-25-2.

Critical Accounting Policies and Significant Judgments and Estimates

The preparation of our consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of our financial statements, as well as the reported revenues and expenses during the reported periods. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

A summary of our significant accounting policies appears in the notes to our audited consolidated financial statements for the year ended December 31, 2017 included in our annual report on Form 10-K. However, we believe that the following accounting policies are important to understanding and evaluating our reported financial results, and we have accordingly included them in this discussion.

Stock-Based Compensation

We have applied the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification Topic 718, *Compensation — Stock Compensation*, or ASC 718, to account for stock-based compensation for employees. We recognize compensation costs related to stock options granted to employees based on the estimated fair value of the awards on the date of grant.

We have equity incentive plans under which various types of equity-based awards including, but not limited to, incentive stock options, non-qualified stock options, and restricted stock awards, may be granted to employees, non-employee directors, and non-employee consultants. We also have an inducement plan under which various types of equity-based awards, including non-qualified stock options and restricted stock awards, may be granted to new employees.

For stock options granted to employees and directors, we recognize compensation expense for all stock-based awards based on the estimated grant-date fair values. For restricted stock awards to employees, the fair value is based on the closing price of the Company's common stock on the date of grant. The value of the portion of the award that is ultimately expected to vest is recognized as expense ratably over the requisite service period. The fair value of stock options is determined using the Black-Scholes option pricing model. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention of paying cash dividends. In connection with the early adoption of ASU 2016-9 in the quarter ended December 31, 2016, we elected an accounting policy to record forfeitures as they occur.

See Note 5, included in Part 1, Item 1 of this quarterly report on Form 10-Q, for a discussion of the assumptions used by the Company in determining the grant date fair value of options granted under the Black-Scholes option pricing model, as well as a summary of the stock option activity under the Company’s stock-based compensation plan for all years presented.

Revenue

In accordance with FASB's ASC 606, *Revenue from Contracts with Customers,* or ASC 606, we recognize revenue when our 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 revenue recognition for arrangements that the Company determines are within the scope of ASC Topic 606, we performs the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

We only apply the five-step model to contracts when we determine that it is probable we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determines those that are performance obligations, and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Amounts received prior to satisfying the revenue recognition criteria are recognized as deferred revenue in our balance sheet. Amounts expected to be recognized as revenue within the twelve months following the balance sheet date are classified as Current portion of deferred revenue. Amounts not expected to be recognized as revenue within the twelve months following the balance sheet date are classified as Deferred revenue, net of current portion.

Alliance Revenues

Our revenues have primarily been generated through licensing arrangements. The terms of these arrangements typically include payment to us of one or more of the following: nonrefundable, up-front license fees; regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under each of our agreements, we perform the following steps:

(i) identification of the promised goods or services in the contract;

(ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract;

(iii) measurement of the transaction price, including the constraint on variable consideration;

(iv) allocation of the transaction price to the performance obligations; and

(v) recognition of revenue when (or as) the Company satisfies each performance obligation.

See Notes 7 and 8, included in Part 1, Item 1 of this quarterly report on Form 10-Q, for additional details surrounding our licensing arrangements.

We also assess whether there is an option in a contract to acquire additional goods or services. An option gives rise to a performance obligation only if the option provides a material right to the customer that it would not receive

without entering into that contract. Factors that we consider in evaluating whether an option represents a material right include, but are not limited to: (i) the overall objective of the arrangement, (ii) the benefit the collaborator might obtain from the arrangement without exercising the option, (iii) the cost to exercise the option (e.g. priced at a significant and incremental discount) and (iv) the likelihood that the option will be exercised. With respect to options determined to be performance obligations, we recognize revenue when those future goods or services are transferred or when the options expire.

Our revenue arrangements may include the following:

Up-front License Fees: If a license is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from nonrefundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone Payments: At the inception of an agreement that includes regulatory or commercial milestone payments, we evaluate whether each milestone is considered probable of being achieved and estimate 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 control of us or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At each reporting period, we assess the probability of achievement of each milestone under our current agreements.

Research and Development Activities: Under our current licensing arrangements, if we are entitled to reimbursement for costs for services we provide, we expect such reimbursement would be an offset to research and development expenses.

Royalties: If we are entitled to receive sales-based royalties from our collaborator, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, provided the reported sales are reliably measurable, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Manufacturing Supply and Research Services: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. We assess if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations.

We receive payments from our licensees based on schedules established in each contract. Upfront payments are recorded as deferred revenue upon receipt, and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Amounts are recorded as accounts receivable when our right to consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Recent Accounting Pronouncements

See Note 2, included in Part 1, Item 1 of this quarterly report on Form 10-Q for information on recent accounting pronouncements.

JOBS Act

The Jumpstart Our Business Startups Act of 2012, or the JOBS Act, contains provisions that, among other things, reduce reporting requirements for an "emerging growth company." As an emerging growth company, we have elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new

or revised accounting standards and, as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies.

Results of Operations

Comparison of the three and six months ended June 30, 2018 and 2017 (in thousands)

	Three Months Ended June 30,			Six Months Ended June 30,		
	2018	2017	Change	2018	2017	Change
Revenue	$ 2,500	$ —	$ 2,500	$ 2,500	$ —	$ 2,500
Operating expenses:						
General and administrative	5,926	4,385	1,541	10,998	9,264	1,734
Research and development	5,128	15,499	(10,371)	9,726	31,595	(21,869)
Restructuring	41	—	41	64	—	64
Total operating expenses	11,095	19,884	(8,789)	20,788	40,859	(20,071)
Loss from operations	(8,595)	(19,884)	11,289	(18,288)	(40,859)	22,571
Other income (expense):						
Change in fair value of warrant liability	4	19	(15)	4	56	(52)
Net gain (loss) on asset disposals	(107)	1	(108)	116	1	115
Miscellaneous income	500	—	500	1,428	628	800
Interest income	226	163	63	425	337	88
Interest expense	(597)	(731)	134	(1,275)	(1,309)	34
Gain on foreign currency exchange	10	—	10	10	—	10
Total other income	36	(548)	584	708	(287)	995
Loss before income tax expense	(8,559)	(20,432)	11,873	(17,580)	(41,146)	23,566
Foreign income tax expense	(745)	—	(745)	(745)	—	(745)
Net loss attributable to common stockholders	$(9,304)	$(20,432)	$ 11,128	$(18,325)	$(41,146)	$ 22,821

Revenue

The revenue recognized primarily relates to the upfront payments received at inception of the agreements.

General and administrative expense

General and administrative expenses consist principally of salaries and related costs for personnel in our executive, finance, commercial, and other administrative areas, including stock-based compensation and travel expenses. Other general and administrative expenses include professional fees for legal, market research, consulting, and accounting services.

General and administrative expenses increased by $1.5 million and $1.7 million, or 35% and 19%, for the three and six months ended June 30, 2018, respectively, as compared to the same periods in 2017, primarily related to employee separation payments, an increase in market research expenditures associated with launch readiness, and increased rent and related expenditures associated with the relocation of our corporate headquarters to Chesterbrook, Pennsylvania in July 2017.

Research and development expense

Research and development expenses consist primarily of costs incurred for research and the development of our product candidates. In addition, research and development expenses include salaries and related costs for our research and development personnel and stock-based compensation expense and travel expenses for such individuals.

Research and development costs are expensed as incurred and are tracked by discovery program and subsequently by product candidate once a product candidate has been selected for development. We record costs for some development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or information provided to us by our vendors.

In October 2017, we announced a restructuring and reduction in force of 21 employees, primarily in the research and development area, as well as other cost saving initiatives.

Research and development expenses decreased by $10.4 million and $21.9 million, or 67% and 69%, for the three and six months ended June 30, 2018, respectively, as compared to the same periods in 2017. The following table summarizes our research and development expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Personnel-related costs	$ 2,132	$ 3,478	$ 4,409	$ 7,174
Oliceridine	2,050	9,670	3,428	20,426
TRV027	6	20	33	113
TRV250	775	898	1,471	1,341
Other research and development	165	1,433	404	2,541
	$ 5,128	$ 15,499	$ 9,745	$ 31,595

The decrease in research and development expenses in 2018 was primarily attributable to the completion of the oliceridine Phase 3 clinical program in 2017, and to a decrease in expenditures resulting from the October 2017 restructuring and reduction in force and associated decrease in research and laboratory-related costs.

Liquidity and Capital Resources

Since inception, we have financed our operations primarily through private placements and public offerings of our equity securities, debt borrowings and payments received under collaboration agreements. At June 30, 2018, we had an accumulated deficit of $375.8 million, working capital of $47.5 million, cash and cash equivalents of $24.0 million, restricted cash of $1.4 million, and marketable securities of $39.5 million.

Cash Flows

The following table summarizes our cash flows for the six months ended June 30, 2018 and 2017 (in thousands):

	Six Months Ended June 30,	
	2018	2017
Net cash (used in) provided by:		
Operating activities	$ (15,743)	$ (47,748)
Investing activities	9,981	13,778
Financing activities	13,242	23,960
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 7,480	$ (10,010)

Net cash used in operating activities

Net cash used in operating activities was $15.7 million for the six months ended June 30, 2018 and consisted primarily of a net loss of $18.3 million and changes in operating assets and liabilities. Changes in prepaid expenses and other assets, accounts payable and accrued expenses result from timing differences between the receipt and payment of cash and when the transactions are recognized in our results of operations. Deferred revenue relates to our ex-U.S. licensing activities in China.

Net cash used in operating activities was $47.7 million for the six months ended June 30, 2017 and consisted primarily of a net loss of $41.1 million and a decrease in accounts payable and accrued expenses of $9.6 million, primarily associated with the completion of the Phase 3 APOLLO-1 and APOLLO-2 studies of oliceridine. Changes in accounts payable and accrued expenses result from timing differences between the receipt and payment of cash and when the transactions are recognized in our results of operations.

Net cash used in investing activities

Net cash used in investing activities was $10.0 million for the six months ended June 30, 2018 and $13.8 million for the six months ended June 30, 2017. Investing activities in both periods consisted primarily of purchases and maturities of marketable securities.

Net cash provided by financing activities

Net cash provided by financing activities was $13.2 million for the six months ended June 30, 2018, which was primarily due to net proceeds of $19.5 million from the sale of common stock through our at-the-market, or ATM, sales facility with Cowen and Company, LLC, or Cowen, offset by principal repayments on our Term Loans of $6.3 million.

Net cash provided by financing activities was $24.0 million for the six months ended June 30, 2017, which was primarily due to net proceeds of $9.9 million from the March 31, 2017 draw of Term Loan C and net proceeds of $13.7 million from the sale of common stock through our ATM sales facility with Cowen.

Operating and Capital Expenditure Requirements

We have not achieved profitability since our inception and we expect to continue to incur net losses and negative cash flows from operations for the foreseeable future. We expect our cash expenditures to continue to be significant in the near term as we prepare for future regulatory activities, and continue clinical development of TRV250. Additionally, over the next twelve months, we anticipate that our payroll and other general and administrative expenses will increase as we prepare for commercial operations, particularly with respect to expenses associated with the selling and marketing of oliceridine, if approved by the FDA.

We believe that our cash and cash equivalents and marketable securities as of June 30, 2018, together with interest thereon, as well as proceeds from the sale of shares of common stock under our $50 million ATM sales facility with Cowen, and from ex-U.S. licensing activities in China between June 30, 2018 and the date of this filing, to be sufficient to fund our operating expenses and capital expenditure requirements for at least twelve months following the date of this filing. If approved by FDA on November 2, 2018, and following DEA Scheduling, we expect to launch oliceridine in the United States in the first half of 2019. The extent of our commercial efforts for oliceridine, including the number of sales representatives and medical science liaisons at launch, will depend to a significant extent on the success of our fundraising efforts between the date of this filing and the launch date. In all cases, we anticipate that we will need to raise substantial additional financing in the future to fund our operations. To meet these requirements, we may seek to sell equity or convertible securities in public or private transactions that may result in dilution to our stockholders. In June 2018, we filed a $175 million shelf registration statement that includes a $50 million ATM sales facility with Cowen acting as our sales agent. As of June 30, 2018, the entire $50 million remained available under the ATM sales facility. We may offer and sell shares of our common stock under the existing registration statement (including under our ATM facility) or any registration statement we may file in the future. If we raise additional funds through the issuance of convertible securities, these securities could have rights senior to those of our common stock and could contain covenants that restrict our operations.

Ultimately, there can be no assurance that we will be able to obtain additional equity or debt financing on terms acceptable to us, if at all. Our future capital requirements will depend on many factors, including:

- the costs, timing and outcome of regulatory review of the oliceridine NDA or any future product candidates, both in the United States and in territories outside the United States;
- the costs, timing, and extent of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

- the scope, progress, results and costs of researching and developing our product candidates or any future product candidates, both in the United States and in territories outside the United States;
- the number and development requirements of any other product candidates that we may pursue;
- our ability to enter into collaborative agreements for the development and/or commercialization of our product candidates, including for oliceridine;
- any product liability or other lawsuits related to our products;
- the expenses needed to attract and retain skilled personnel;
- the costs involved in preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending our intellectual property-related claims, both in the United States and in territories outside the United States.

Please see "Risk Factors" section of this Quarterly Report, for additional risks associated with our substantial capital requirements.

Contractual Obligations and Commitments

The following is a summary of our long-term contractual cash obligations as of June 30, 2018 (in thousands):

	Payments Due By Period				
	Total	Less than 1 Year	1 – 3 years	3 – 5 years	More than 5 years
Operating lease obligations(1)	$ 13,633	$ 824	$ 2,704	$ 2,802	$ 7,303
Loans payable	24,048	12,667	11,381	—	—
Purchase Obligations	2,312	2,312	—	—	—
Total	$ 39,993	$ 15,803	$ 14,085	$ 2,802	$ 7,303

(1) Operating lease obligations reflect our obligation to make payments in connection with the leases for our office spaces, including our current location in Chesterbrook, Pennsylvania and our previous location in King of Prussia, Pennsylvania.

Other Commitments

In addition, in the course of normal business operations, we have agreements with contract service providers to assist in the performance of our research and development and manufacturing activities. We can elect to discontinue the work under these agreements at any time. We also could enter into additional collaborative research, contract research, manufacturing and supplier agreements in the future, which may require upfront payments and even long-term commitments of cash.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States of America, or GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reported period. In accordance with GAAP, we base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

Please see the "Critical Accounting Policies and Significant Judgments and Estimates" section of our most recent Annual Report on Form 10-K as filed with the SEC which is incorporated herein by reference, for full detail. Except for the added disclosures related to Alliance revenue in Note 2, included in Part 1, Item 1 of this quarterly report

on Form 10-Q, we did not make any significant changes to our critical accounting policies during the six months ended June 30, 2018.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, as defined by applicable SEC regulations.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations.

We had cash and cash equivalents of $24.0 million and marketable securities of $39.5 million at June 30, 2018, consisting primarily of funds in cash, money market funds, U.S. Treasury and U.S. government agency securities. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 10% increase or decrease in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

ITEM 4. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Interim Principal Financial Officer and Accounting Officer, evaluated the effectiveness of our disclosure controls and procedures as of June 30, 2018, the end of the period covered by this Quarterly Report on Form 10-Q.

Based on our evaluation, we believe that our disclosure controls and procedures as of the date of our Quarterly Report on Form 10-Q have been designed and are functioning effectively to provide reasonable assurance that the information required to be disclosed by us in reports filed under the Securities Exchange Act of 1934 is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. We believe that a controls system, no matter how well designed and operated, cannot provide absolute assurance that the objectives of the controls system are met, and no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within a company have been detected.

Our independent registered public accounting firm has not performed an evaluation of our internal control over financial reporting during any period in accordance with the provisions of the Sarbanes-Oxley Act. As a result, it is possible that, had our independent registered public accounting firm performed an evaluation of our internal control over financial reporting in accordance with the provisions of the Sarbanes-Oxley Act, material weaknesses and significant control deficiencies may have been identified. However, for as long as we remain an "emerging growth company" as defined in the JOBS Act, we intend to take advantage of the exemption permitting us not to comply with the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II

ITEM 1. LEGAL PROCEEDINGS

The Company is not involved in any legal proceeding that it expects to have a material effect on its business, financial condition, results of operations and cash flows.

ITEM 1A. RISK FACTORS

Our business is subject to numerous risks. You should carefully consider the following risks and all other information contained in this Quarterly Report on Form 10-Q, as well as general economic and business risks, together with any other documents we file with the SEC. If any of the following events actually occur or risks actually materialize, it could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our common stock to decline.

Risks Related to Our Financial Position and Capital Needs

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 $18.3 million for the six months ended June 30, 2018, and $71.9 million, $103.0 million, and $50.5 million for the years ended December 31, 2017, 2016, and 2015, respectively. As of June 30, 2018, we had an accumulated deficit of $375.8 million. To date, we have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. We have devoted substantially all of our financial resources and efforts to research and development, including nonclinical studies and clinical trials. We still have not completed development of any of our 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 as we:

- establish sales, marketing and distribution capabilities and scale up external manufacturing capabilities to commercialize oliceridine, if approved, and any other products that we choose not to license to a third party and for which we may obtain regulatory approval;
- conduct clinical trials for TRV250, our δ-receptor product candidate, as well as any additional clinical trials of oliceridine that may be required by FDA;
- seek to identify additional product candidates;
- conduct clinical trials and seek regulatory approvals for any product candidates that successfully complete clinical trials;
- maintain, expand, and protect our intellectual property portfolio;
- hire additional sales, marketing, medical, clinical and scientific personnel; and
- add operational, financial, and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

To become and remain profitable, we must succeed in raising substantial additional funding for the Company and developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing nonclinical testing and clinical trials of our product candidates, identifying additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates, and manufacturing, marketing, and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of some of these activities and have not begun others. We may never succeed in these activities and, even if we do, may never 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, whether we will have sufficient funding available to or when, or if, we will be able to achieve profitability. If we are required by the FDA or foreign regulatory authorities, to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials, making necessary regulatory filings, or the development of any of our product candidates, our expenses could increase. During the first half of 2019, assuming FDA approval on November 2, 2018 and Drug Enforcement Administration, or DEA, scheduling, we expect to launch oliceridine in the United States. The extent of our commercial efforts for oliceridine, including the number of sales representatives and medical science liaisons at launch, will depend to a significant extent on the success of our fundraising efforts between the date of this filing and the launch date. Absent substantial additional fundraising, the level and extent of our commercial efforts may lead to a delay in our ability to achieve profitability.

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

We will need substantial additional funding, which may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Over the next several years, we expect to incur significant expenses in connection with our current operations and the servicing and repayment of our outstanding debt obligations. In preparation for the potential regulatory approval of oliceridine, we expect to incur significant expenses related to our product manufacturing, marketing, sales, and distribution efforts. Accordingly, we will need to obtain substantial additional funding for these efforts and for the continued repayment of our outstanding term loans through the March 2020 maturity date; we would seek to obtain this funding through the sale of equity, debt financings, and/or other sources, including potential collaborations. Ultimately, we may be unable to raise additional funds or enter into such other arrangements when needed, on favorable terms, or at all. If we fail to raise additional capital or enter into such arrangements as, and when, needed, we could be forced to:

- significantly delay, scale back, or discontinue our operations, development programs, and/or any future commercialization efforts;
- relinquish, or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves;
- seek collaborators for one or more of our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- cease operations altogether.

We estimate that our existing cash and cash equivalents and marketable securities as of June 30, 2018, together with interest thereon, as well as proceeds from the sale of shares of common stock under the Company's at the market, or ATM, sales agreement with Cowen and Company, LLC, or Cowen, and from ex-U.S. licensing activities in China between June 30, 2018 and the date of this filing to be sufficient to fund its operating expenses and capital expenditure requirements for at least twelve months following the date of this filing. If we are unable to raise additional funds prior to this date, or we do not take steps to reduce our expenses, our lenders may conclude that there has been a material adverse change in the Company's financial condition, or a material impairment in the value of the loan collateral or in the prospect of repayment of our obligations to the lenders. In this case, the lenders have the right to foreclose on the available collateral, including our cash and cash equivalents and marketable securities.

The extent of our future capital requirements will depend on many factors, including:

- the costs, timing, and outcome of regulatory review of the oliceridine NDA or any future product candidates, both in the United States and in territories outside the United States;

- 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 revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the scope, progress, results and costs of nonclinical development, laboratory testing, and clinical trials for our other product candidates, including TRV250;
- the number and development requirements of other product candidates that we pursue;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates, including oliceridine;
- any product liability or other lawsuits related to our products;
- the expenses needed to attract and retain skilled personnel; and
- the costs involved in preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property rights, and defending any intellectual property-related claims, both in the United States and in territories outside the United States.

Identifying potential product candidates and conducting nonclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. Despite these efforts, 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 or meet our expectations. Our commercial revenue, if any, will be derived from sales of products that we do not expect to be commercially available until, at the earliest, the first half of 2019, 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.

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

Until such time, if ever, as we can generate substantial product revenue and positive cash flows from operations, we expect to finance our cash needs through a combination of equity offerings, debt financings, and license and development agreements in connection with any collaborations. 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, your ownership interest will be diluted, either at the time of such capital raise or thereafter, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Preferred equity financing and additional debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, or declaring dividends.

If we raise additional funds through 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 you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in late 2007, and our activities to date have been limited to, among other things, organizing and staffing our company, business planning, raising capital, developing our product platform,

identifying potential product candidates, undertaking nonclinical studies, and conducting clinical trials. With the exception of oliceridine, our product candidates are early in development. We have not yet demonstrated our ability to obtain regulatory approvals, manufacture a product at commercial scale or arrange for a third party to do so on our behalf, or conduct sales, marketing, and distribution activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as reliable as they could be if we had a longer operating history.

In addition, as a young business, we may encounter unforeseen expenses, difficulties, complications, delays, and other known and unknown factors. We will need to significantly expand our capabilities to support future activities related to the approval, manufacture, and commercialization of our product candidates. We may be unsuccessful in adding such capabilities.

We expect our financial condition and operating results to continue 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, you should not rely upon the results of any past quarterly or annual periods as indications of future operating performance.

Risks Related to Regulatory Approval 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 timely commercialize, or to commercialize at all, 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, 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 the United States. Failure to obtain marketing approval for our product candidates will prevent us from commercializing these product candidates and will significantly limit our ability to generate revenue in the future. To date, we have not received approvals to market any of our product candidates from regulatory authorities in any jurisdiction and we may never be successful in obtaining any such approvals.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals, and we have relied and expect to continue to rely on third parties to assist us in this process. Securing marketing approval requires the submission of extensive nonclinical 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. 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. For oliceridine, we have submitted an NDA to the FDA. The FDA has indicated to us that the Prescription Drug User Fee Act review date for the NDA is November 2, 2018. It is possible that FDA may not meet this target date for any number of reasons, including if it considers the submission of additional information or data during the review process to constitute a major amendment to the NDA. Ultimately, the oliceridine NDA may not be approved by or on the November 2, 2018 target date, if at all.

The FDA also has indicated to us that it expects to convene an Advisory Committee as part of the review process, which we currently expect will be held in October 2018. The Advisory Committee will discuss and advise FDA on the risk-benefit profile of oliceridine. In advance of this Advisory Committee meeting, we and the FDA will submit briefing documents for the committee's review, and these briefing documents will be made available to the public and may include information from the oliceridine development program that have not previously been disclosed. Historically, for some companies, disclosure of information in this manner has led to increased volatility in their stock

price. The Advisory Committee and FDA may interpret nonclinical and clinical data differently than we and our experts have or conclude that there is not sufficient nonclinical and/or clinical data to support approval of our NDA. Across the Phase 3 clinical development program for oliceridine, there were three Suspected Unexpected Serious Adverse Reactions, or SUSARs, reported to the FDA: one each for instances of post-operative ileus and lethargy, and one patient who experienced hepato-renal failure. All cases resolved without clinical sequelae. While we believe these events are consistent with the presumed mechanism of action of oliceridine or with the clinical context of the surgical patient population included in the Phase 3 study program, the Advisory Committee and FDA may disagree with our interpretations and conclusions. Furthermore, press coverage and public scrutiny of the materials that will be discussed at the Advisory Committee meeting may negatively affect the potential for our NDA to receive approval, particularly in light of the current nationwide focus on opioids. Even if we ultimately obtain approval of the NDA, the matters discussed at the Advisory Committee meeting could limit our ability to successfully commercialize oliceridine.

The feedback received from an Advisory Committee can have a substantial impact on the FDA's decision to approve or reject an NDA. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional nonclinical studies or clinical trials, among other things. In addition, varying interpretations of the data obtained from nonclinical and clinical testing, including from our ATHENA Phase 3 open label safety study, QTc interval study, renal impairment study, or other Phase 1, 2 or 3 clinical studies, 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.

We have submitted to the FDA a proposed proprietary name for oliceridine and we are awaiting feedback. FDA will only approve a tradename, if at all, when approving the NDA. If we experience delays in obtaining approval of our NDA, the commercial prospects for our product candidates may be harmed and our ability to generate revenue may be materially impaired. Furthermore, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications, dosages, or presentations than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate or that includes language, such as a black box warning, that may impair our ability to successfully commercial that product candidate. Any of these scenarios could negatively impact the commercial prospects for our product candidates or our ability to raise sufficient capital to support our operations in the future.

Our μ opioid receptor targeted product candidates, including oliceridine, may require Risk Evaluation and Mitigation Strategies, which could delay the approval of these product candidates and increase the cost, burden and liability associated with the commercialization of these product candidates.

Risk Evaluation and Mitigation Strategy, or REMS, are imposed by FDA to assure safe use of the product candidates, either as a condition of product candidate approval or on the basis of new safety information. Our μ opioid receptor product candidates, including oliceridine, if approved, may require a REMS, and it is possible that our other product candidates may require a REMS. The REMS may include medication guides for patients, special communication plans to health care professionals or elements to assure safe use such as restricted distribution methods, patient registries and/or other risk minimization tools. We cannot predict the specific REMS that may be required as part of the FDA's approval of our product candidates. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription, or dispensing of our product candidates, if approved. Depending on the extent of the REMS requirements, these requirements may significantly increase our costs to commercialize these product candidates and could negatively affect sales. Furthermore, risks of our product candidates that are not adequately addressed through proposed REMS for such product candidates also may prevent or delay their approval for commercialization.

Our μ opioid receptor targeted product candidates, including oliceridine, are expected to be classified as controlled substances, the making, use, sale, importation, exportation and distribution of which are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies.

Our μ opioid receptor targeted product candidates, including oliceridine, are likely to be classified as controlled substances, which are subject to state, federal and foreign laws and regulations regarding their manufacture, use, sale,

importation, exportation and distribution. Controlled substances are regulated under the Federal Controlled Substances Act of 1970, or CSA, and regulations of the DEA.

The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. We expect oliceridine to be regulated by the DEA as a Schedule II controlled substance.

Various states also independently regulate controlled substances. Though state controlled substances laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule drugs as well. While some states automatically schedule a drug when the DEA does so, in other states there must be rulemaking or a legislative action. State scheduling may delay commercial sale of any controlled substance drug product for which we obtain federal regulatory approval and adverse scheduling could impair the commercial attractiveness of such product. We or our collaborators must also obtain separate state registrations in order to be able to obtain, handle and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions from the states in addition to those from the DEA or otherwise arising under federal law.

For any of our product candidates classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. There is a risk that DEA regulations may limit the supply of the compounds used in clinical trials for our product candidates, and, in the future, the ability to produce and distribute our products in the volume needed to both meet commercial demand and build inventory to mitigate possible supply disruptions.

Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, recordkeeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of product candidates including controlled substances. The DEA, and some states, conduct periodic inspections of registered establishments that handle controlled substances. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of their restrictive nature, these regulations could limit commercialization of any of our product candidates that are classified as controlled substances.

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

To market and sell our products in the European Union, Asia, and many other jurisdictions, we, our current collaborators in South Korea and China for oliceridine, or any future 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 the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside 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 collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

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 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 ongoing 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. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The FDA also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for only their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care 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 yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters;
- 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 revenue;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing

requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

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.

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. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue 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, safety and potential advantages compared to alternative treatments;
- the timing of market introduction of the product candidate as well as competitive products;
- our ability to offer the product for sale profitably and at competitive prices;
- 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 level and extent of sales, marketing, and distribution support;
- the availability of third party coverage and adequate reimbursement;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved; and
- any restrictions on the use of our products, both on their own and together with other medications.

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

We currently have limited resources focused on the manufacturing, marketing, sales, and distribution of pharmaceutical products and have limited experience and capabilities in this area. To commercialize any product candidates that receive marketing approval, we would need to build manufacturing, marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If we successfully develop and obtain regulatory approval for any of our product candidates, we expect to build or outsource a targeted specialist sales force to market or co-promote the product in the United States; we currently do not expect to build sales, manufacturing and distribution capabilities outside of the United States, although this expectation could change in the future. There are substantial risks involved with establishing 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 is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred certain commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

There are a number of factors that may inhibit our efforts to commercialize our products on our own, including:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel or to outsource these tasks to a third party;

- the inability of sales personnel to obtain access to physicians or other relevant personnel or educate adequate numbers of physicians or others on the benefit of our future products;

- the lack of complementary or other products to be offered by sales personnel, which may put us at a competitive disadvantage from the perspective of sales efficiency relative to companies with more extensive product lines; and

- unforeseen costs and expenses associated with creating a sales and marketing organization.

As an alternative to establishing our own sales force, we may choose to partner with third parties that have well-established direct sales forces to sell, market and distribute our products, particularly in markets outside of the United States. If we are unable to enter into collaborations with third parties for the commercialization of approved products, if any, on acceptable terms or at all, or if any such partner does not devote sufficient resources to the commercialization of our product or otherwise fails in commercialization efforts, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval.

For oliceridine, we will need to partner with one or more third parties to sell, market and distribute this product, if approved, outside the United States. In April 2018 and May 2018, we entered into exclusive licensing agreements for the development and commercialization of oliceridine in South Korea and China, respectively. Such partnerships in South Korea and China may not be successful, and we may be unsuccessful in our efforts to secure additional partnerships outside the United States.

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. In addition to existing therapeutic treatments for the indications we are targeting with our product candidates, if any of our product candidates achieves regulatory approval, we also face potential competition from other drug candidates in development by other companies. Oliceridine also may compete against, or be used in combination with, OFIRMEV® (IV acetaminophen), marketed by Mallinckrodt plc, with EXPAREL® (liposomal bupivacaine), marketed by Pacira Pharmaceuticals, Inc., CALDOLOR® (IV ibuprofen), marketed by Cumberland Pharmaceuticals, DYLOJECT™ (IV diclofenac), and marketed by Hospira. In addition to currently marketed IV analgesics, we are aware of a number of products in development that are aimed at improving the treatment of moderate-to-severe acute pain. AcelRx Pharmaceuticals, Inc. is developing a range of acute pain products involving sufentanil oral nanotabs in hand-held dispensers including DSUVIA™ and ZALVISO™. Innocoll Holdings plc, and Heron Therapeutics Inc. have proprietary long-acting reformulations of bupivacaine in development. Recro Pharma, Inc. is developing an IV version of the NSAID meloxicam. Cara Therapeutics Inc. is developing IV and oral dose forms of a peripherally restricted κ-opioid receptor agonist, which has been administered in combination with μ-opioids in clinical trials. Avenue Therapeutics, Inc. is developing an IV version of the generic opioid tramadol for moderate-to-severe acute pain. Some of these potential competitive compounds are being developed by large, well-financed, and experienced pharmaceutical and biotechnology companies, or have been partnered with such companies, which may give them development, regulatory and marketing advantages over us.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we 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 our competitors establishing a strong 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 the indications that we are pursuing. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competing generic products.

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

products. 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 also may 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.

Even if we or any future collaborators are able to commercialize any of our product candidates, the product candidates may become subject to unfavorable pricing regulations, third party coverage and reimbursement policies, healthcare reform initiatives, or regulatory or political concerns.

Both our and our collaborators' ability to commercialize any of our product candidates successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government payor programs at the federal and state level, including Medicare and Medicaid, private health insurers, managed care plans 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. In addition, for hospital products, a private health insurer or Medicare will typically reimburse a fixed fee for certain procedures, including in-patient surgeries. Pharmaceutical products such as oliceridine, if approved, that may be used in connection with the surgery generally will not be separately reimbursed and, therefore, a hospital would have to assess the cost of oliceridine, if approved, relative to its benefits. Current or future efforts to limit the level of reimbursement for in-patient hospital procedures could cause a hospital to decide not to use oliceridine, if approved by the FDA. 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 or procedures. 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 drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement for a product or procedure may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any product candidate for which we or our collaborators obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to seek 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 or our collaborators may not be able to successfully commercialize any product candidates for which marketing approval is obtained.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or analogous regulatory authorities outside 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, also may 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 or our collaborators' inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved drugs that we develop could adversely affect our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs 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 licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay commercial launch of the drug, possibly for lengthy time periods, and negatively impact our ability to generate revenue from the sale

of the drug 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.

In addition to the above factors, the approval and commercialization of oliceridine may be negatively impacted by changing perceptions in the United States and elsewhere among regulators, legislators, and the general public concerning the approval, use, and abuse of prescription opioid products. In the future, the FDA and other regulatory and legislative bodies may enact regulations that seek to limit opioid prescribing and use. In response to these efforts and changing perceptions, physicians may determine to reduce the volume of opioid prescriptions they prescribe to patients. Any of these changes could negatively impact both the timing and likelihood of FDA approval of oliceridine, as well as the commercial opportunity, if approved.

There can be no assurance that our product candidates, 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, that they will be considered cost-effective by third party payors, that coverage or an adequate level of reimbursement will be available, or that third party payors' reimbursement policies will not adversely affect our ability to profitably sell our product candidates if they are approved for sale.

Product liability lawsuits against us could cause us to incur substantial liabilities and 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 will face an even greater risk if we commercially sell any products that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. 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;
- initiation of investigations by regulators;
- significant costs to defend the related litigation;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- 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 maintain $15 million in product liability insurance coverage, which may be inadequate to cover all liabilities that we may incur. We will likely 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, and in the future may be difficult to obtain for products such as oliceridine. 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 the Discovery and Development of Our Product Candidates

Our research and development efforts have been focused on discovering and developing novel drugs based on biased ligands, and the approach we are taking to discover and develop drugs is not proven and may never lead to marketable products.

The development of drugs based on biased ligands is an emerging field, and the scientific discoveries that form the basis for our historical efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing differentiated product candidates based on these discoveries is both preliminary and limited. We believe that we are the first company to conduct a clinical trial of a product candidate based on the concept of biased ligands. Therefore, we do not know if our approach will be successful or will ultimately lead to the approval of any current or future product candidate.

We are early in our development efforts and have only one product candidate, oliceridine, for which we have submitted an NDA to the FDA. If we are unable to successfully complete development and commercialization of our product candidates, either on our own or with a partner, or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts and have only one product candidate, oliceridine, for which we have completed Phase 3 development and submitted an NDA to the FDA. To this point, we have invested substantially all of our efforts and financial resources in the identification and development of biased ligands. Our ability to generate product revenue, which we do not expect will occur until, at the earliest, the first quarter of 2019, 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:

- successful completion of nonclinical studies and clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- obtaining, maintaining, and protecting our intellectual property portfolio, including patents and trade secrets, and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of our products, if and when approved, by patients, the medical community, and third party payors;
- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage of our products and adequate reimbursement; and
- maintaining a continued acceptable safety profile of our 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 commercialize our product candidates, which would materially harm our business.

We may not be successful in our efforts to expand our pipeline of product candidates.

One element of our strategy has been to expand our pipeline of therapeutics based on biased ligands and advance these product candidates through clinical development for the treatment of a variety of indications. Until recently, we maintained an active discovery research effort. In October 2017, we made the decision to halt our early stage research, although we continue to assess the future development of a series of novel S1P modulators. Without internal discovery research capabilities, we will need to expand our pipeline through other means, including, for example, by in-licensing product candidates for further development. We may not be able to identify, acquire, and

develop product candidates that are safe and effective. Even if we are successful in continuing to expand our pipeline, the potential product candidates that we identify or in-license 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, we will not be able to obtain product revenue in future periods, which would make it unlikely that we would ever achieve profitability.

Nonclinical and 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.

Clinical testing is expensive, can take many years to complete, and has a high risk of failure. 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 nonclinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. A failure of one or more clinical trials can occur at any stage of testing. The outcome of nonclinical 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, nonclinical and clinical data often are susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. We may experience numerous unforeseen events during, or as a result of, clinical trials, which could delay or prevent our ability to receive marketing approval or subsequently to commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at prospective trial sites;
- 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;
- 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 a finding that the participants are being exposed to unacceptable health risks;
- regulators or institutional review boards 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;
- 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; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

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 that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing and/or reporting requirements; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs also will increase if we experience delays in testing or in receiving marketing approvals. We do not know whether any of our nonclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant nonclinical 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, thereby harming 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 the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, 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 other factors including:

- the severity of the disease under investigation;
- the eligibility criteria for the study in question;
- the perceived risks and benefits of the product candidate under study;
- 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; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. 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 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 are associated with adverse side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the side effects or other characteristics are less prevalent, less severe, or more acceptable from a risk-benefit

perspective. In our industry, many compounds that initially showed promise in early stage testing have later been found to cause side effects that prevented further development of the compound or significantly limited its commercial opportunity. Across the Phase 3 clinical development program for oliceridine, there were three SUSARs reported to the FDA: one each for instances of post-operative ileus and lethargy, and one patient who experienced hepato-renal failure. In the event that our clinical trials reveal a high and unacceptable severity and prevalence of side effects, our trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development or deny approval of our product candidates for any or all targeted indications. Drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial and could result in potential product liability claims.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may require additional warnings on the label or even withdraw approvals of such product;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients, if one is not required in connection with regulatory approval;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved.

Oliceridine is predominantly metabolized by two liver enzymes, CYP2D6 and CYP3A4, that are common metabolic pathways for drugs. Because of competitive use of these pathways, we may need to conduct additional drug interaction studies and oliceridine may be limited in its co-administration with other drugs using these pathways as their safety and effectiveness, as well as oliceridine's, may be adversely affected. This could limit our commercial opportunity due to the common co-administration of drugs in patients with moderate-to-severe acute pain requiring IV therapy. In addition, since CYP2D6 enzyme activity varies in the population, different dosing may be required in the product label for individuals that have low levels of CYP2D6 activity, which could limit the commercial opportunity of the drug, if approved. We continue to discuss this question with the FDA and cannot assure you that the FDA will not require us to utilize different dosing for this population and/or prospectively characterize individuals' CYP2D6 activity prior to administering oliceridine.

Oliceridine and TRV734 are both biased ligands targeted at the μ-opioid receptor. Common adverse reactions for agonists of the μ-opioid receptor include respiratory depression, constipation, nausea, vomiting, and addiction. In rare cases, μ-opioid receptor agonists can cause respiratory arrest requiring immediate medical intervention. Since oliceridine and TRV734 also modulate the μ-opioid receptor, these adverse reactions and risks likely will apply to the use of oliceridine and TRV734. One healthy subject in the 0.25 mg dosing cohort of our Phase 1 clinical trial of oliceridine experienced a severe episode of vasovagal syncope during which he fainted and his pulse stopped. These were considered severe adverse events. It is possible that serious adverse vasovagal events could occur in other patients dosed with oliceridine. Agonists at the δ-opioid receptor have been associated with a risk of seizures. TRV250, our δ-opioid receptor product candidate, targets the same receptor as other programs that have been associated with seizures and, accordingly, it is possible that it will be associated with similar side effects. In such case, we likely would discontinue further development of TRV250 for the treatment of migraines.

We may expend our limited resources to pursue a particular product candidate or indication and thereby fail to capitalize on other 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 fewer clinical or regulatory risks and/or greater

commercial potential. 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.

Risks Related to Our Dependence on Third Parties

Our current collaborators are, and any future relationships or collaborations we may enter into may be, important to us. If we are unable to maintain our relationship with any of these collaborations, or if our relationship with these collaborators is not successful, our business could be adversely affected.

We have limited capabilities for product development, sales, marketing, and distribution. For our product candidates, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of these candidates. For oliceridine, we recently entered into license agreements with partners in South Korea and China whereby these parties will develop, seek regulatory approval for, and, if successful, commercialize oliceridine. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. 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 and our business may be materially and adversely affected.

Any future collaborations we might enter into with another third party, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may elect not to continue development or commercialization programs or may not pursue commercialization of any product candidates that achieve regulatory approval based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that 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 limit or eliminate efforts and resources to the commercialization of our product candidates;

- 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 proprietary rights, contract interpretation, or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

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

- collaborations may be terminated at 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.

If any collaborations we might enter into in the future 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 platform and product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. The risks relating to our product development, regulatory approval and commercialization described in this Annual Report also apply to the activities of our therapeutic program collaborators.

If a future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate 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 reputation in the business and financial communities could be adversely affected.

We rely, and expect to continue to rely, on third parties to conduct our nonclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or complying with applicable regulatory requirements.

We rely on third parties, such as contract research organizations, clinical research organizations, clinical data management organizations, medical institutions, and clinical investigators to conduct our nonclinical studies and clinical trials for our product candidates. The agreements with these third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that could delay our product development activities.

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 nonclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our nonclinical studies are conducted in accordance with good laboratory practice, or GLP, as appropriate. 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. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators, and trial sites. If we or any of our clinical research organizations fail to comply with applicable GCPs, the clinical data

generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practice, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. 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.

The third parties with whom we have contracted to help perform our nonclinical studies or clinical trials also may have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or conduct our nonclinical studies or 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 commercialize our product candidates.

If any of our relationships with these third party contract research organizations or clinical research organizations terminate, we may not be able to enter into arrangements with alternative contract research organizations or clinical research organizations or to do so on commercially reasonable terms. Switching or adding additional contract research organizations or clinical research organizations involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new contract research organization or clinical research organization commences work. As a result, delays could occur that could compromise our ability to meet our desired development timelines. Although we seek to carefully manage our relationships with our contract research organizations and clinical research organizations, there can be no assurance that we will not encounter similar challenges or delays in the future.

We contract with third parties for the manufacture of our product candidates for nonclinical 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, which could delay, prevent or impair our development or commercialization efforts.

We have limited internal manufacturing capabilities and do not have any manufacturing facilities. In addition, our product candidates have never been manufactured at commercial scale. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for nonclinical 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 product candidates for which our collaborators or we 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;
- manufacturing delays if our third party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- 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.

The facilities used by our contract manufacturers to manufacture our product candidates and, potentially in the future, our products must be approved by the FDA pursuant to inspections that will be conducted after we submit an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with current cGMP regulations for manufacture of our product candidates. Third party manufacturers may not be able to comply with the cGMP regulations or similar regulatory requirements outside 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 commercialize likely will 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. We may incur added costs and delays in identifying and qualifying any replacement manufacturers.

The U.S. Drug Enforcement Administration, or DEA, restricts the importation of a controlled substance finished drug product when the same substance is commercially available in the United States, which could reduce the number of potential alternative manufacturers for our μ-opioid receptor targeted product candidates, including oliceridine. In addition, a DEA quota system controls and limits the availability and production of controlled substances and the DEA also has authority to grant or deny requests for quota of controlled substances, which will likely include the active ingredients in oliceridine. Supply disruptions could result from delays in obtaining DEA approvals for controlled substances or from the receipt of quota of controlled substances that are insufficient to meet future product demand. The quota system also may limit our ability to build inventory as a method for mitigating possible supply disruptions if oliceridine is approved for sale in the United States.

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 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 rely on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable.

As part of our strategy to mitigate development risk, we seek to develop product candidates with validated mechanisms of action and we utilize biomarkers to assess potential clinical efficacy early in the development process. This strategy necessarily relies upon clinical data and other results obtained by third parties that may ultimately prove to be inaccurate or unreliable. Further, such clinical data and results may be based on products or product candidates that are significantly different from our product candidates. If the third party data and results we rely upon prove to be inaccurate, unreliable or not applicable to our product candidates, we could make inaccurate assumptions and conclusions about our product candidates and our research and development efforts could be compromised.

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute 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. Should we enter into collaborations with third parties, we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical 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 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. 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 a first filing, or in some cases at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, 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 or narrow the scope of our patent protection.

The Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith Act was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent and Trademark Office continues to develop and implement new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, 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 and financial condition.

Moreover, we may be subject to a third party preissuance submission of prior art to the United States Patent and Trademark Office, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, render unenforceable, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us, or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent does not foreclose challenges to its inventorship, scope, validity or enforceability. Therefore, our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our

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

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

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, rendered unenforceable, or interpreted narrowly.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights that are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

Third parties may initiate legal proceedings alleging that we are infringing 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 the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceedings before the United States Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

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

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 currently party to license agreements for technologies that we use in conducting our drug discovery activities. In the future, we may become party to licenses that are important for product development and commercialization. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product or utilize any technology that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially and adversely affect the value of a product candidate being developed under any such agreement or could restrict our drug discovery activities. 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.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

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

In addition, while it is our policy to require our employees 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 and their assignment agreements 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.

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. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation 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. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

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

In addition to seeking patent protection for our product candidates, we rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We limit disclosure of such trade secrets where possible, but we also seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who do have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside 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, 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, our competitive position would be harmed.

Risks Related to Legal Compliance Matters

Our current and future relationships with customers and third party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations, which 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 in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third party payors, and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which we conduct research, sell, market, and distribute any drugs 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. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which 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 of, any good or service, for which payment may be made under federal and state healthcare programs, such as Medicare and Medicaid;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes, among other things, 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, or HITECH, and their respective implementing regulations, which impose, among other things, obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Open Payments program, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to "payments or other transfers of value" made to physicians, which is defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and teaching hospitals and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members, requirements for manufacturers to submit reports to CMS by the 90th day of each calendar year, and subsequent disclosure of such information by CMS on a publicly available website; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or

marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may 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, including, without limitation, damages, fines, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which also could materially affect our business.

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.

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.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality, and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. 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, or collectively, the PPACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% commencing January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain

individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- the new requirements under the federal Open Payments program and its implementing regulations;
- 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.

Some of the provisions of the PPACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the PPACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the PPACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the PPACA or otherwise circumvent some of the requirements for health insurance mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-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, or the BBA, among other things, amends the PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole".

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for 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.

It is possible that healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the reimbursement that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the 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 the United States tend to impose strict price controls, which may adversely affect our revenue, 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 coverage and 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 fail to comply with environmental, health, and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health, and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. 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. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, 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.

Risks Related to Employee Matters and Managing Our 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 development, clinical, business development, legal, financial, and commercial expertise of our executive officers. Although we have entered into employment agreements with these individuals, 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 management, scientific, clinical, manufacturing, sales and marketing, and other personnel also will be critical to our success. Maxine Gowen, Ph.D., our President and Chief Executive Officer,

will retire on October 1, 2018. The board of directors selected Carrie L. Bourdow, who currently serves as our Executive Vice President and Chief Operating Officer, to be our next President and Chief Executive Officer, effective October 1, 2018. On June 11, 2018, the board of directors appointed John P. Hamill, who currently serves as a consultant to us, as our interim Principal Financial Officer and Principal Accounting Officer. The board of directors has not yet identified a candidate to serve as our Principal Financial Officer and Principal Accounting Officer on a permanent basis. The loss of the services of our executive officers or other key employees or consultants could impede the achievement of our development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees or consultants 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, clinical, and commercial advisors, to assist us in formulating our 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, regulatory, manufacturing, 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 growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, manufacturing, 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.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could expose us to liability and hurt our reputation.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct also could involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. 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 or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including the imposition of significant fines or other sanctions.

Other Risks Related to our Business

We intend to conduct a substantial portion of the clinical trials for our product candidates outside of the United States and, if approved, we intend to seek to market our product candidates abroad through third party collaborators. Accordingly, we will be subject to the risks of doing business outside of the United States.

We intend to conduct a substantial portion of our clinical trials outside of the United States and, if approved, we intend to seek to market our product candidates outside of the United States. We are thus subject to risks associated with doing business outside of the United States. With respect to our product candidates, we may choose to partner with third

parties that have direct sales forces and established distribution systems, in lieu of our own sales force and distribution systems, which would indirectly expose us to these risks. Our business and financial results in the future could be adversely affected due to a variety of factors associated with conducting development and marketing of our product candidates, if approved, outside of the United States, including:

- efforts to develop an international sales, marketing and distribution organization may increase our expenses, divert our management's attention from the development of product candidates or cause us to forgo profitable licensing opportunities in these geographies;
- changes in a specific country's or region's political and cultural climate or economic condition;
- unexpected changes in foreign laws and regulatory requirements;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- inadequate intellectual property protection in foreign countries;
- differing payor reimbursement regimes, governmental payors or patient self-pay systems and price controls;
- trade-protection measures, import or export licensing requirements such as Export Administration Regulations promulgated by the U.S. Department of Commerce and fines, penalties or suspension or revocation of export privileges;
- regulations under the U.S. Foreign Corrupt Practices Act and similar foreign anti-corruption laws;
- the effects of applicable foreign tax structures and potentially adverse tax consequences; and
- significant adverse changes in foreign currency exchange rates which could make the cost of our clinical trials, to the extent conducted outside of the United States, more expensive.

Our business and operations would suffer in the event of system failures.

We utilize information technology systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data. There can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects.

Despite our implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption to our product candidate development programs. For example, the loss of clinical trial data from completed, ongoing or planned 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 personal, confidential or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed or abandoned.

Risks Related to Ownership of Our Common Stock

An active trading market for our common stock may not continue to develop or be sustained.

Although our common stock is listed on the NASDAQ Global Select Market, or NASDAQ, we cannot assure you that an active, liquid trading market for our shares will 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 you to sell shares quickly or without depressing the market price for the shares or to sell your shares at all.

The trading price of the shares of our common stock has been and may continue to be volatile, and you may not be able to resell some or all of your shares at a desired price.

Since our common stock commenced trading in January 2014, our stock price has been highly volatile, with closing stock prices ranging from a high of $13.30 per share to a low of $1.34 per share as of August 1, 2018.

The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors in our stock may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- actual or anticipated variations in our operating results;
- changes in financial estimates by us or by any securities analysts who might cover our stock;
- the timing and results of our clinical trials for any of our product candidates;
- failure or discontinuation of any of our development programs;
- conditions or trends in our industry;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry;
- announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- recruitment or departure of key personnel;
- announcements and expectations of additional financing efforts; and
- sales of our common stock, including sales by our directors and officers or specific stockholders.

In addition, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from the operation of our business.

If equity research analysts do not continue to publish research or reports or publish unfavorable research or reports about us, our business or our industry, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. As a relatively new public company, we have only limited research coverage by equity research analysts. Equity research analysts may elect not to initiate or continue to provide research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. We have no control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research.

If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

Sales of a substantial number of shares of our common stock 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 could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

In addition, we have filed registration statements on Form S-8 registering the issuance of shares of common stock subject to options or other equity awards issued or reserved for future issuance under our equity incentive plans. Shares registered under these registration statements on Form S-8 are available for sale in the public market subject to vesting arrangements and exercise of existing options, the grant of new options in the future, and the restrictions of Rule 144 in the case of our affiliates.

The issuance of additional stock in connection with financings, acquisitions, investments, our stock incentive plans or otherwise will dilute all other stockholders.

Our amended and restated certificate of incorporation authorizes us to issue up to 200,000,000 shares of common stock and up to 5,000,000 shares of preferred stock with such rights and preferences as may be determined by our board of directors. Subject to compliance with applicable rules and regulations, we may issue our shares of common stock or securities convertible into our common stock from time to time in connection with a financing, acquisition, investment, our stock incentive plans or otherwise. Any such issuance could result in substantial dilution to our existing stockholders and cause the trading price of our common stock to decline.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history. We do not anticipate generating revenue from sales of products for the foreseeable future, if ever, and we may never achieve profitability. To the extent that we continue to generate tax losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have not completed our analysis to determine what, if any, impact any prior ownership change has had on our ability to utilize our net operating loss carryforwards. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As of June 30, 2018, we had federal net operating loss carryforwards of approximately $62.1 million that could be limited if we have experienced, or if in the future we experience, an ownership change.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our board of directors has the authority to issue up to 5,000,000 shares of preferred stock. The board of directors can fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

Our charter documents also contain other provisions that could have an anti-takeover effect, including:

- only one of our three classes of directors will be elected each year;

- stockholders are not entitled to remove directors other than by a 66 2/3% vote and only for cause;
- stockholders are not permitted to take actions by written consent;
- stockholders cannot call a special meeting of stockholders; and
- stockholders must give advance notice to nominate directors or submit proposals for consideration at stockholder meetings.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Our executive officers, directors and current beneficial owners of 5% or more of our common stock and their respective affiliates, in the aggregate, beneficially own a majority of our outstanding common stock. As a result, these persons, acting together, would be able to control all matters requiring stockholder approval, including the election and removal of directors, the approval of any merger, consolidation, sale of all or substantially all of our assets, or other significant corporate transactions.

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, 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 cannot predict if investors will find our common stock less attractive because we will 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. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earliest of (a) December 31, 2019, (b) the last day of the fiscal year in which we have total annual gross revenue of at least $1.0 billion, (c) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (d) any date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

Under Section 107(b) of the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

We are subject to the reporting requirements of the Securities Exchange Act of 1934, the Sarbanes-Oxley Act and the rules and regulations of NASDAQ. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal controls over financial reporting. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. For our fiscal year ended December 31, 2018, we are obligated to

perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Form 10-K filing for that year, as required by Section 404(a) of the Sarbanes-Oxley Act. We will continue to incur substantial additional professional fees and internal costs to expand our accounting and finance functions and expend significant management efforts. We may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all error and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404(a) of the Sarbanes-Oxley Act in a timely manner, or if we are unable to implement or maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our stock could decline and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the Securities and Exchange Commission, or SEC, or other regulatory authorities. In addition, any testing by us conducted in connection with Section 404(a) of the Sarbanes-Oxley Act, or the subsequent testing by our independent registered public accounting firm conducted in connection with Section 404(b) of the Sarbanes-Oxley Act once we no longer qualify as an "emerging growth company," may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses; or may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement.

We are required to disclose changes made in our internal control procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404(b). If and when we cease to be an "emerging growth company," an assessment of the effectiveness of our internal controls by our independent registered public accounting firm will be very expensive and could detect problems that our management's assessment might not.

Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

You should not rely on an investment in our common stock to provide dividend income. We have not declared or paid cash dividends on our common stock to date and have no plans to pay cash dividends in the foreseeable future. We currently intend to retain our future earnings, if any, to fund the development and growth of our business. In addition, the terms of our term loan credit facility with Oxford Finance LLC and Pacific Western Bank prohibits us from paying cash dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

We incur costs and demands upon management as a result of being a public company.

As a public company listed in the United States, we are incurring, and will continue to incur, significant legal, accounting and other costs, particularly after we cease to be an "emerging growth company." These costs could negatively affect our financial results. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the SEC and stock exchanges, may increase legal and financial compliance costs and make some activities more time consuming. These laws, regulations and standards are subject to varying interpretations and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If, notwithstanding our efforts to comply with new laws, regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

Failure to comply with these rules also might make it more difficult for us to obtain some types of insurance, including directors' and officers' liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also

make it more difficult for us to attract and retain qualified persons to serve on our board of directors, on committees of our board of directors or as members of senior management.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

None.

ITEM 3. DEFAULTS UPON SENIOR SECURITIES

None.

ITEM 4. MINE SAFETY DISCLOSURES

None.

ITEM 5. OTHER INFORMATION

None.

ITEM 6. EXHIBITS

The following is a list of exhibits filed as part of this Quarterly Report on Form 10-Q.

Exhibit Number	Description
3.1	Certificate of Amendment of Amended and Restated Certificate of Incorporation of Trevena, Inc. (incorporated by reference to Exhibit 3.1 to Registrant's Current Report on Form 8-K, filed with the SEC on May 21, 2018).
10.1	Common Stock Sales Agreement, dated June 15, 2018, by and between Trevena, Inc. and Cowen and Company, LLC (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on June 15, 2018).
31.1#	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
31.2#	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
32.1*#	Certification of the 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 the 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#	The following financial information from this Quarterly Report on Form 10-Q for the three and six months ended June 30, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of June 30, 2018 and December 31, 2017, (ii) Statements of Operations and Comprehensive Income (Loss) for the three and six months ended June 30, 2018 and 2017, (iii) Statement of Stockholders' Equity for the period from January 1, 2018 to June 30, 2018, (iv) Statements of Cash Flows for the six months ended June 30, 2018 and 2017 and (v) Notes to Unaudited Financial Statements, tagged as blocks of text.

* These certifications are being furnished solely to accompany this quarterly report pursuant to 18 U.S.C. Section 1350, and are not being filed for purposes of Section 18 of the Exchange Act and are not to be incorporated by reference into any filing of the registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

\# Filed herewith.

EXHIBIT INDEX

Exhibit Number	Description
31.1	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
31.2	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
32.1*	Certification of the 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 the 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	The following financial information from this Quarterly Report on Form 10-Q for the three and six months ended June 30, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of June 30, 2018 and December 31, 2017, (ii) Statements of Operations and Comprehensive Income (Loss) for the three and six months ended June 30, 2018 and 2017, (iii) Statement of Stockholders' Equity for the period from January 1, 2018 to June 30, 2018, (iv) Statements of Cash Flows for the six months ended June 30, 2018 and 2017 and (v) Notes to Unaudited Financial Statements, tagged as blocks of text.

* These certifications are being furnished solely to accompany this quarterly report pursuant to 18 U.S.C. Section 1350, and are not being filed for purposes of Section 18 of the Exchange Act and are not to be incorporated by reference into any filing of the registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: August 2, 2018

TREVENA, INC.

By: /s/ JOHN P. HAMILL
John P. Hamill
Interim Principal Financial Officer
and Accounting Officer

Exhibit 31.1

Certification of Principal Executive Officer of Trevena, Inc.
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Maxine Gowen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Trevena, 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the 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 2, 2018

/s/ MAXINE GOWEN
Maxine Gowen
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer of Trevena, Inc.
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, John P. Hamill, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Trevena, 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the 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 2, 2018

/s/ JOHN P. HAMILL
John P. Hamill
Interim Principal Financial Officer
and Accounting Officer

Exhibit 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

In connection with the Quarterly Report of Trevena, Inc. (the "Company") on Form 10-Q for the period ended June 30, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Maxine Gowen, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my 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 of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: August 2, 2018

/s/ MAXINE GOWEN
Maxine Gowen
President and Chief Executive Officer
(Principal Executive Officer)

This certification accompanies the Report and shall not be deemed "filed" by the Company with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Report), irrespective of any general incorporation language contained in such filing.

Exhibit 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

In connection with the Quarterly Report of Trevena, Inc. (the "Company") on Form 10-Q for the period ended June 30, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, John P. Hamill, Interim Principal Financial Officer and Accounting Officer, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my 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 of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Dated: August 2, 2018

/s/ JOHN P. HAMILL
John P. Hamill
Interim Principal Financial Officer
and Accounting Officer

This certification accompanies the Report and shall not be deemed "filed" by the Company with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Report), irrespective of any general incorporation language contained in such filing.