UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2020

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: 001-38886

TREVI THERAPEUTICS, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**45-0834299**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
195 Church Street, 14th Floor New Haven, Connecticut	**06510**
(Address of principal executive offices)	**(Zip Code)**

(203) 304-2499
(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	**TRVI**	**The Nasdaq Stock Market LLC**

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
		Emerging growth company	☒

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

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

As of May 7, 2020, the registrant had 17,834,570 shares of common stock, $0.001 par value per share, outstanding.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Quarterly Report on Form 10-Q contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Quarterly Report on Form 10-Q, including statements regarding our strategy, future operations, future financial position, future revenues and profitability, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would,” “could,” “continue” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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

- the impact of the COVID-19 pandemic on our clinical trials, business and operations;
- our ongoing clinical trials, including our Phase 2b/3 PRISM trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis;
- our plans to develop and, if approved, subsequently commercialize nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for other serious neurologically mediated conditions;
- our expectations regarding the timing for the initiation of clinical trials and the reporting of data from such trials;
- the timing of and our ability to submit applications for, and to obtain and maintain regulatory approvals for nalbuphine ER;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash and cash equivalents;
- our estimates regarding expenses, future revenue, timing of any future revenue, capital requirements and needs for additional financing;
- the impact of government laws and regulations;
- our competitive position; and
- our ability to establish and maintain collaborations or obtain additional funding.

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

You should read this Quarterly Report on Form 10-Q and the documents that we have filed as exhibits to this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results may differ materially from what we expect. The forward-looking statements contained in this Quarterly Report on Form 10-Q are made as of the date of this Quarterly Report on Form 10-Q, and we do not assume any obligation to update any forward-looking statements except as required by applicable law.

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Item 1. Financial Statements.

Trevi Therapeutics, Inc.

Condensed Consolidated Balance Sheets

(unaudited)

(Amounts in thousands, except share and per share amounts)

	March 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 52,640	$ 57,313
Tax credit and other receivables	125	558
Prepaid expenses	1,055	1,681
Total current assets	53,820	59,552
Operating lease right-of-use asset	292	312
Security deposit	19	19
Property, equipment and leasehold improvements, net	107	118
Total assets	$ 54,238	$ 60,001
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,193	$ 1,599
Accrued expenses	4,911	3,501
Operating lease liability - current portion	102	99
Total current liabilities	7,206	5,199
Operating lease liability - long term portion	230	257
Commitments and contingencies (Note 12)		
Stockholders' equity (deficit):		
Common stock: $0.001 par value; 200,000,000 shares authorized at March 31, 2020 and December 31, 2019, respectively; and 17,834,570 shares issued and outstanding at March 31, 2020 and December 31, 2019, respectively.	18	18
Preferred stock: $0.001 par value; 5,000,000 shares authorized at March 31, 2020 and December 31, 2019, respectively; no shares issued or outstanding at March 31, 2020 or December 31, 2019.	—	—
Additional paid-in capital	169,476	168,746
Accumulated deficit	(122,692)	(114,219)
Total stockholders' equity	46,802	54,545
Total liabilities and stockholders' equity	$ 54,238	$ 60,001

See accompanying notes.

Trevi Therapeutics, Inc.

Condensed Consolidated Statements of Operations

(unaudited)

(Amounts in thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2020	2019
Operating expenses:		
Research and development	$ 6,019	$ 3,338
General and administrative	2,620	1,474
Total operating expenses	8,639	4,812
Loss from operations	(8,639)	(4,812)
Other income (expense):		
Change in fair value of obligation for loan success fee	—	(52)
Interest income	157	58
Total other income (expense), net	157	6
Loss before income tax benefit	(8,482)	(4,806)
Income tax benefit	9	4
Net loss	$ (8,473)	$ (4,802)
Accretion of redeemable convertible preferred stock	—	203
Dividends accrued on redeemable convertible preferred stock	—	(1,553)
Adjusted net loss attributable to common stockholders	$ (8,473)	$ (6,152)
Basic and diluted net loss per common share outstanding	$ (0.48)	$ (13.85)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	17,834,570	444,132

See accompanying notes.

Trevi Therapeutics, Inc.

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

(unaudited)

(Amounts in thousands, except share amounts)

	Series A Redeemable Convertible Preferred Stock		Series B Redeemable Convertible Preferred Stock		Series C Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2018	15,387,923	$ 21,033	22,608,695	$ 33,686	38,097,672	$ 61,023	438,600	$ 4	$ —	$ (109,498)	$ (109,494)
Stock-based compensation	—	—	—	—	—	—	—	—	146	—	146
Issuance of common stock from exercise of stock options	—	—	—	—	—	—	7,894	—	24	—	24
Issuance of Series C redeemable convertible preferred stock, net of issuance costs	—	—	—	—	6,849,315	11,059	—	—	—	—	—
Dividends accrued on redeemable convertible preferred stock	—	228	—	384	—	941	—	—	(170)	(1,383)	(1,553)
Accretion (amortization) of premium (discount) on issuance of redeemable convertible preferred stock	—	(1)	—	5	—	—	—	—	—	(4)	(4)
Accretion of discount on investor rights/obligation	—	14	—	20	—	—	—	—		(34)	(34)
Adjustment for excess (shortfall) of fair value over liquidation value of redeemable convertible preferred stock	—	(106)	—	(153)	—	(19)	—	—	—	278	278
Accretion of issuance costs on redeemable convertible preferred stock	—	1	—	1	—	35	—	—		(37)	(37)
Net loss	—	—	—	—	—	—	—	—	—	(4,802)	(4,802)
Balance at March 31, 2019	15,387,923	$ 21,169	22,608,695	$ 33,943	44,946,987	$ 73,039	446,494	$ 4	$ —	$ (115,480)	$ (115,476)
Balance at December 31, 2019	—	$ —	—	$ —	—	$ —	17,834,570	$ 18	$ 168,746	$ (114,219)	$ 54,545
Stock-based compensation	—	—	—	—	—	—	—	—	730	—	730
Net loss	—	—	—	—	—	—	—	—	—	(8,473)	(8,473)
Balance at March 31, 2020	—	$ —	—	$ —	—	$ —	17,834,570	$ 18	$ 169,476	$ (122,692)	$ 46,802

See accompanying notes.

Trevi Therapeutics, Inc.

Condensed Consolidated Statements of Cash Flows

(unaudited)

(Amounts in thousands)

	Three Months Ended March 31,	
	2020	**2019**
Operating activities		
Net loss	$ (8,473)	$ (4,802)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	10	9
Changes in fair value of obligation for loan success fee	—	52
Stock-based compensation	730	146
Changes in operating assets and liabilities:		
Receivables	433	34
Prepaid expenses	626	(230)
Accounts payable	594	(185)
Accrued expenses	1,407	880
Net cash used in operating activities	(4,673)	(4,096)
Investing activities		
Acquisitions of property, equipment and leasehold improvements	—	(9)
Net cash used in investing activities	—	(9)
Financing activities		
Proceeds from exercises of stock options		24
Proceeds from sale of Series C redeemable convertible preferred stock, net of issuance costs	—	9,963
Deferred offering costs	—	(138)
Net cash provided by financing activities	—	9,849
Net cash increase (decrease)	(4,673)	5,744
Cash and cash equivalents at beginning of period	57,313	7,202
Cash and cash equivalents at end of period	$ 52,640	$ 12,946
Supplemental disclosure of non-cash financing activities		
Deferred offering costs	$ —	$ (214)
Dividends accrued on redeemable convertible preferred stock	$ —	$ 1,553
Accretion on redeemable convertible preferred stock	$ —	$ (203)

See accompanying notes.

1. Nature of the Business

Trevi Therapeutics, Inc. ("Trevi" or the "Company") is a clinical-stage biopharmaceutical company focused on the development and commercialization of nalbuphine ER to treat serious neurologically mediated conditions. The Company is currently developing nalbuphine ER for the treatment of chronic pruritus, chronic cough in patients with idiopathic pulmonary fibrosis ("IPF"), and levodopa-induced dyskinesia ("LID") in patients with Parkinson's disease. These conditions share a common pathophysiology that is mediated through opioid receptors in the central and peripheral nervous systems. Due to nalbuphine's mechanism of action as a modulator of opioid receptors, the Company believes nalbuphine ER has the potential to be effective in treating each of these conditions.

Nalbuphine ER is an oral extended release formulation of nalbuphine. Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the United States and Europe. The κ- and μ-opioid receptors are known to be critical mediators of itch, cough and certain movement disorders. Nalbuphine's mechanism of action also mitigates the risk of abuse associated with μ-opioid agonists because it antagonizes, or blocks, the μ-opioid receptor. Nalbuphine is currently the only opioid approved for marketing that is not classified as a controlled substance in the United States and most of Europe.

On April 22, 2019, the Company filed an amendment to the Company's amended and restated certificate of incorporation to effect a one-for 9.5 reverse stock split of the Company's common stock, which resulted in a proportional adjustment to the existing conversion ratios for each series of the Company's redeemable convertible preferred stock. Accordingly, all share and per share amounts in the condensed consolidated financial statements have been retrospectively adjusted, where applicable, to reflect the effect of the reverse stock split and adjustments of the redeemable convertible preferred stock conversion for all periods presented.

On May 9, 2019, the Company completed its initial public offering ("IPO") and a concurrent private placement in which it issued and sold an aggregate of 7,000,000 shares of common stock at an offering price of $10.00 per share, for net proceeds of $62.1 million, after deducting aggregate underwriting discounts and commissions and private placement agent fees of $4.9 million and other offering expenses of $3.0 million. The Company's common stock began trading on The Nasdaq Global Market on May 7, 2019 under the ticker symbol "TRVI".

Upon the closing of the IPO, the Company's outstanding redeemable convertible preferred stock, including the accrued dividends thereon, automatically converted into shares of the Company's common stock. Upon such conversion of the redeemable convertible preferred stock, the Company reclassified the carrying values of the redeemable convertible preferred stock to common stock and additional paid-in capital.

The accompanying financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Since inception, the Company has financed its operations primarily through private placements of its redeemable convertible preferred stock and convertible notes as well as borrowings under a term loan facility, and most recently, with proceeds from the IPO and concurrent private placement completed in May 2019. The Company has incurred recurring losses since inception, including net losses attributable to the Company of $8.5 million for three months ended March 31, 2020 and $26.1 million for the year ended December 31, 2019. In addition, as of March 31, 2020, the Company had an accumulated deficit of $122.7 million. The Company expects to continue to generate operating losses for the foreseeable future. As of May 7, 2020, the issuance date of these Condensed Consolidated Financial Statements, the Company expects that its cash and cash equivalents of $52.6 million as of March 31, 2020, will be sufficient to fund its operating expenses and capital expenditure requirements through at least 12 months from the date of issuance of these Condensed Consolidated Financial Statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying unaudited interim condensed consolidated financial statements for the three months ended March 31, 2020 and 2019 included herein, have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") for interim financial information and to the rules and regulations of the Securities and Exchange Commission ("SEC") for interim information. Certain information and footnote disclosure typically prepared in accordance with GAAP have been condensed or omitted pursuant to SEC rules and regulations. The accompanying unaudited condensed consolidated financial statements and notes should be read in conjunction with the audited consolidated financial statements and related notes for the year ended December 31, 2019 included in the Company's Annual Report on Form 10-K for the year ended December 31, 2019 (the "Annual Report on Form 10-K"). In the opinion of management, the unaudited condensed consolidated financial statements reflect all adjustments, which include normal recurring adjustments necessary for the fair presentation of the Company's interim financial statements presented. The results of operations for the interim periods are not necessarily indicative of the results expected for the full year or any subsequent period.

The accompanying Condensed Consolidated Financial Statements include the accounts of Trevi Therapeutics, Inc. and its wholly-owned subsidiary Trevi Therapeutics Limited. Intercompany balances and transactions have been eliminated.

All amounts presented are in thousands of dollars, except share and per share amounts, unless noted otherwise. The Company has evaluated events occurring subsequent to March 31, 2020 for potential recognition or disclosure in the Condensed Consolidated Financial Statements and concluded there were no subsequent events that required recognition or disclosure other than those provided.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of the expenses during the reporting periods. Significant estimates and assumptions reflected in these Condensed Consolidated Financial Statements include, but are not limited to the recognition of research and development ("R&D") expenses and the valuation of redeemable convertible preferred stock, common stock and stock-based awards. On an ongoing basis, management evaluates its estimates in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Unaudited Interim Financial Information

The accompanying interim Condensed Consolidated Balance Sheet as of March 31, 2020, the Condensed Consolidated Statements of Operations and the Condensed Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit) for the three months ended March 31, 2020 and 2019, and the Condensed Consolidated Statements of Cash Flows for the three months ended March 31, 2020 and 2019 are unaudited. The unaudited interim Condensed Consolidated Financial Statements have been prepared on the same basis as the audited annual consolidated financial statements and, in the Company's opinion, reflect all adjustments, which include only normal recurring adjustments, necessary for the fair statements of its financial position as of March 31, 2020, the results of its operations for the three months ended March 31, 2020 and 2019, and its cash flows for the three months ended March 31, 2020 and 2019. The results for the three months ended March 31, 2020 and 2019 are not necessarily indicative of results to be expected for the year ending December 31, 2020, any other interim period, or any future year or period.

Fair Value Measurements

The Company's financial instruments have consisted of cash and cash equivalents, tax credit and other receivables, accounts payable, accrued expenses and obligation for loan success fee *(Note 6)*. Fair value estimates of these instruments are made at a specific point in time, based on relevant market information. The carrying amounts of cash and cash equivalents, tax credit and other receivables, accounts payable and accrued expenses are generally considered to be representative of their respective fair values because of the short term nature of those instruments.

Current accounting guidance defines fair value, establishes a framework for measuring fair value in accordance with Accounting Standards Codification ("ASC") 820, *Fair Value Measurements and Disclosures*, and requires certain disclosures about fair value measurements. The valuation techniques included in the guidance are based on observable and unobservable inputs. Observable inputs reflect readily obtainable data from independent sources, while unobservable inputs reflect market assumptions and are classified into the following fair value hierarchy:

Level 1—Observable inputs—quoted prices in active markets for identical assets and liabilities.

Level 2—Observable inputs other than the quoted prices in active markets for identical assets and liabilities—such as quoted prices for similar instruments, quoted prices for identical or similar instruments in inactive markets, or other inputs that are observable or can be corroborated by observable market data.

Level 3—Unobservable inputs—includes amounts derived from valuation models where one or more significant inputs are unobservable and require the company to develop relevant assumptions.

There were no fair value financial assets or liabilities as of March 31, 2020.

The following table represents a roll-forward of the fair value of Level 3 instruments (significant unobservable inputs):

Financial liabilities		
Beginning balance at January 1, 2019[(1)]	$	1,556
Unrealized loss on Series C redeemable convertible preferred stock liability		—
Unrealized loss on obligation for loan success fee		215
Net settlements[(2)]		(1,771)
Ending balance at December 31, 2019	$	—

(1) The balance at January 1, 2019 relates to the $460 obligation for the loan success fee and the $1,096 fair value of the Series C redeemable convertible preferred stock liability at the time of the third tranche of the Series C Preferred Stock financing in January 2019.

(2) The net settlements for the year ended December 31, 2019 relate to the $1,096 fair value of the Series C redeemable convertible preferred stock liability at the time of the third tranche of the Series C Preferred Stock financing in January 2019 and the payment of the $675 obligation for the loan success fee in May 2019.

Deferred Offering Costs

The Company capitalizes certain legal, professional, accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of an equity financing, these costs are recorded in stockholders' equity (deficit) as a reduction of additional paid-in capital generated as a result of the offering. Should the planned equity financing no longer be considered probable of being consummated, the deferred offering costs are expensed immediately as a charge to operating expenses. The Company's IPO was completed in May 2019 and IPO costs incurred in 2019 were recorded as a reduction to stockholders' equity (deficit). As a result, as of March 31, 2020 and December 31, 2019, the Company did not have any deferred offering costs.

Basic and Diluted Net Income (Loss) per Common Share

Basic and diluted net loss per common share outstanding is determined by dividing net loss, as adjusted for accretion and accrued dividends on redeemable convertible preferred stock, by the weighted average common shares outstanding during the period. For all periods presented, outstanding shares of Series A redeemable convertible preferred stock ("Series A Preferred Stock"), shares of Series B redeemable convertible preferred stock ("Series B Preferred Stock"), shares of Series C Preferred Stock, if any, and shares issuable upon exercise of stock options have been excluded from the calculation because their effects would be anti-dilutive. Therefore, the weighted average common shares used to calculate both basic and diluted net loss per share are the same for each of the periods presented.

Recently Adopted Accounting Pronouncements

There have been no new accounting pronouncements adopted during the three months ended March 31, 2020.

Recently Issued Accounting Pronouncements

There have been no new accounting pronouncements during the three months ended March 31, 2020, as compared to the recent accounting pronouncements described in Note 2 to the Company's audited consolidated financial statements for the year ended December 31, 2019 included in the Annual Report on Form 10-K, which could be expected to materially impact the Company's unaudited Condensed Consolidated Financial Statements.

3. Prepaid Expenses

Prepaid expenses consist of the following:

	As of March 31, 2020	As of December 31, 2019
Prepaid R&D payments	$ 770	$ 1,113
Prepaid corporate insurance	151	491
Other	134	77
	$ 1,055	$ 1,681

4. Leases

Effective March 1, 2013, the Company entered into a lease for office space in New Haven, CT and commencing March 1, 2018, the Company entered into the First Amendment to the lease. The leased space approximates 5,600 square feet and the lease has a term of 60 months. The lease requires monthly payments ranging from approximately $10 to $11 through February 1, 2023 and provides for two designated months of free rent. The Company has the option to terminate the lease after 36 months by providing six months notice along with a payment to the landlord in an amount representing the unamortized cost of tenant improvements plus the unamortized broker's commission, both of which had been paid by the landlord, and as defined in the agreement.

Under ASC 842, the Company determines if an arrangement is a lease at its inception. If an operating lease has a term greater than one year, the lease is recognized in the balance sheet as a right-of-use asset and an operating lease liability at lease commencement. The Company elected the short-term lease practical expedient; therefore, if an operating lease has a term less than one year, the Company will not recognize the lease on its balance sheet. The operating right-of-use asset represents the Company's right of use to an underlying asset for the term of the lease, and the operating liability represents the Company's obligation to make lease payments arising from the lease.

Operating lease right-of-use assets and operating lease liabilities are determined and recognized on the commencement date of the lease based on the present value of lease payments over the term of the lease. As the Company's leases do not provide an implicit rate within the lease, the Company uses its incremental borrowing rate, which is updated periodically, based on information available at the commencement date of the lease to determine the present value of the lease payments. The incremental borrowing rate used on existing leases as of March 31, 2020 was 13.0%. The right-of-use asset also includes any lease payments related to initial direct costs and prepayments, and excludes lease incentives. Lease expense is recognized on a straight line basis over the lease term. The Company had no new leases during the three months ended March 31, 2020.

The Company's operating leases consist of real estate and equipment, and have remaining terms ranging from approximately 1 to 4 years. The Company has no financing leases. The following table summarizes the Company's operating leases as presented on its Condensed Consolidated Balance Sheet:

	As of March 31, 2020	As of December 31, 2019
Assets:		
Operating lease right-of-use asset	$ 292	$ 312
Liabilities:		
Operating lease liabilities, current portion	102	99
Operating lease liabilities, long term portion	230	257
Total operating lease liabilities	$ 332	$ 356

Future minimum lease payments under the operating leases are as follows as of March 31, 2020:

	As of March 31, 2020
2020	$ 104
2021	138
2022	131
2023	24
Total lease payments	397
Less: imputed discount rate	(65)
Carrying value of operating lease liabilities	$ 332

Lease expense under operating leases, including leases of office equipment, was $34 and $31 for the three months ended March 31, 2020 and 2019, respectively. Lease payments made in the three months ended March 31, 2020 and 2019 were $45 and $35, respectively, with such amounts reflected in the Condensed Consolidated Statement of Cash Flows in operating activities.

5. Accrued Expenses

Accrued expenses consist of the following:

	As of March 31, 2020	As of December 31, 2019
Accrued research projects	$ 3,736	$ 2,084
Accrued professional fees	388	338
Accrued compensation and benefits	565	776
Other	222	303
	$ 4,911	$ 3,501

6. Term Loan Payable

On December 29, 2014, the Company entered into a loan and security agreement (the “Loan Agreement”) with Solar Capital, Ltd. (“Solar”) and Square 1 Bank (“Square 1”), together (the “Lenders”), which provided $15.0 million in debt financing (the “Term Loan”). On June 29, 2018, the maturity date of the Loan Agreement, the Company made its final payments of principal and interest due to the Lenders in connection with the Term Loan, as well as $450 in full payment of the final fee and $82 in full payment of the amendment fee. As a result, there were no outstanding borrowings under the Term Loan as of March 31, 2020 or December 31, 2019, and the Company’s obligations to the Lenders under the Loan Agreement, other than the obligations under the Success Fee Agreement as described below, were terminated.

Under the terms of the Loan Agreement, the Company was obligated to pay the Lenders a Success Fee (“Success Fee”) under a Success Fee Agreement (“Success Fee Agreement”) upon the first occurrence of an Exit Event, as defined. The Exit Event included, among other things, the completion of a public offering of common stock. The amount of the Success Fee was equal to 4.5% of the $15.0 million Term Loan funded. The Success Fee Agreement was scheduled to terminate on the earlier to occur of (a) payment in full of the Success Fee pursuant to its terms, or (b) December 29, 2021. The completion of the IPO on May 9, 2019 (see Note 1) triggered the Success Fee payment obligation and the Company made payments to its Lenders totaling $675 in May 2019. Upon such payments, the Success Fee Agreement terminated.

The Success Fee Agreement represented a free-standing financial instrument. Accordingly, the Company accounted for the Success Fee provision as a derivative under ASC 815, Derivatives and Hedging, and therefore recorded an obligation for the Success Fee at its fair value on the closing date of each advance under the Loan Agreement. Upon recording such obligations for the Success Fee, the Company also recorded an offsetting loan discount, which was accreted to interest expense in the Company's Statements of Operations through the Term Loan's maturity date. The Company adjusted these liabilities for the Success Fee to fair value at each reporting date they remained outstanding. As discussed above, the Success Fee was paid in May 2019; and therefore, the total fair value of the Success Fee liabilities was $0 at March 31, 2020. The total fair value of these liabilities was determined to be $512 at March 31, 2019. The Company recorded non-cash charges in the amount of $0 and $52 for the three months ended March 31, 2020 and 2019, respectively, representing the changes in the fair value of these liabilities since their last measurement date. The fair values of the obligation for the Success Fee were estimated utilizing a probability-weighted income approach, including variables for the timing of the success event and other probability estimates. The non-cash charges are included in other income (expense) in the Company's Condensed Consolidated Statements of Operations.

7. Common Stock

As of March 31, 2020 and December 31, 2019, the Company's certificate of incorporation, as amended and restated, authorized the Company to issue 200,000,000 shares of common stock, respectively, with a par value of $0.001 per share.

As of March 31, 2020 and December 31, 2019, the Company had reserved 3,670,540 shares and 2,778,812 shares of common stock, respectively, for the exercise of outstanding stock options and the number of shares of common stock remaining available for future stock-based awards under the Company's 2012 Stock Incentive Plan, 2019 Stock Incentive Plan and 2019 Employee Stock Purchase Plan, as shown in the table below (*Note 8*):

	March 31, 2020	December 31, 2019
Shares of common stock reserved for future issuance under the 2012 Stock Incentive Plan	1,043,992	1,043,992
Shares of common stock reserved for future issuance under the 2019 Stock Incentive Plan	2,293,097	1,579,714
Shares of common stock reserved for future issuance under the 2019 Employee Stock Purchase Plan	333,451	155,106
	3,670,540	2,778,812

8. Stock-Based Awards

In April 2019, the Company's board of directors adopted the 2019 Stock Incentive Plan (the "2019 Plan"), which became effective on May 7, 2019. The 2019 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The Company's employees, officers, directors, consultants and advisors are eligible to receive awards under the 2019 Plan. The 2019 Plan is administered by the Company's board of directors.

As of March 31, 2020, awards may be made under the 2019 Plan for up to such number of shares of the Company's common stock as is equal to the sum of i) 1,578,947 shares; plus ii) the number of shares (up to 1,157,894 shares) equal to the number of shares of the Company's common stock subject to outstanding awards under the Company's 2012 Stock Incentive Plan (the "2012 Plan"), as amended that expire, terminate or are otherwise cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right; plus iii) an annual increase to be added on the first day of each fiscal year, beginning with 2020 and continuing through 2029, equal to the least of (a) 2,105,623 shares of common stock, (b) 4% of the number of outstanding shares of the Company's common stock on such date, and (c) an amount determined by the Company's board of directors. The number of shares reserved for issuance under the 2019 Plan increased, pursuant to the terms of the 2019 Plan, by an additional 713,383 shares, equal to 4% of the Company's then-outstanding Common Stock, effective as of January 1, 2020.

The 2012 Plan was adopted by the Company's board of directors and stockholders. The Company's board of directors administers the 2012 Plan. The 2012 Plan provides for the issuance of stock-based awards to the Company's employees, officers and directors, as well as non-employee/consultants and advisors to the Company.

Options granted under the 2019 Plan and the 2012 Plan have a maximum term of ten years. Options vest over four years based on varying vesting schedules including: 25% vesting on the first anniversary date of grant and the balance ratably over the next 36 months or vesting in equal monthly or quarterly installments over four years. As of March 31, 2020 and December 31, 2019, respectively, options to purchase 1,161,543 shares and 631,234 shares of common stock were granted and outstanding, net of cancelations, under the 2019 Plan. As of March 31, 2020 and December 31, 2019, respectively, options to purchase 1,043,992 shares of common stock were granted and outstanding, net of cancelations, under the 2012 Plan.

In April 2019, the Company's board of directors adopted a resolution effective on May 7, 2019 that no further stock options or other equity-based awards may be granted under the 2012 Plan.

During the three months ended March 31, 2019, no stock options were granted.

During the three months ended March 31, 2019, options granted were exercised for 7,894 shares of common stock.

During the three months ended March 31, 2019, stock options to purchase 10,197 shares of the Company's common stock were forfeited.

A summary of the Company's combined stock option activity for the 2019 Plan and the 2012 Plan for the three months ended March 31, 2020 is as follows:

	Number of Option Shares	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2019	1,675,226	$ 6.20	7.8	$ 864
Granted	530,309	$ 5.50		
Forfeited	—	$ —		
Expired	—	$ —		
Exercised	—	$ —		
Outstanding as of March 31, 2020	2,205,535	$ 6.03	8.1	$ 512
Options exercisable as of March 31, 2020	742,947	$ 3.34	6.0	$ 502
Options unvested as of March 31, 2020	1,462,588	$ 7.40	9.2	$ 10

The following table summarizes the classifications of stock-based compensation expenses for the 2012 Plan and the 2019 Plan recognized in the Condensed Consolidated Statements of Operations:

	Three Months Ended March 31,	
	2020	2019
Research and development expense	$ 93	$ 22
General and administrative expense	637	124
	$ 730	$ 146

In April 2019, the Company's board of directors adopted the 2019 Employee Stock Purchase Plan (the "2019 ESPP"), which became effective on May 7, 2019. The 2019 ESPP is administered by the Company's board of directors. As of March 31, 2020, there has been no activity under the 2019 ESPP.

As of March 31, 2020, the number of shares of the Company's common stock that has been reserved to be issued under the 2019 ESPP is equal to the sum of i) 155,106 shares plus ii) an annual increase to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2020 and continuing for each fiscal year until, and including, the fiscal year ending December 31, 2029, equal to the least of (a) 526,315 shares of common stock, (b) 1% of the number of outstanding shares of the Company's common stock on such date, and (c) an amount determined by the Company's board of directors. The number of shares of the Company's common stock reserved for issuance under the 2019 ESPP increased, pursuant to the terms of the 2019 ESPP, by an additional 178,345 shares, equal to 1% of the Company's then-outstanding common stock, effective as of January 1, 2020.

All of the Company's employees are eligible to participate in the 2019 ESPP, provided that:

- such person is customarily employed by the Company for more than 20 hours a week and for more than five months in a calendar year;
- such person has been employed by the Company for at least three months prior to enrolling in the 2019 ESPP; and
- such person was an employee of the Company on the first day of the applicable offering period under the 2019 ESPP.

9. Income Taxes

During the three months ended March 31, 2020 and 2019, the Company maintained a full valuation allowance on deferred tax assets. Therefore, the Company has not recorded a provision for income taxes.

10. Net Loss per Share

The following table summarizes the computation of basic and diluted net loss per share attributable to common stockholders of the Company:

	Three Months Ended March 31,	
	2020	2019
Net loss	$ (8,473)	$ (4,802)
Plus: Accretion of redeemable convertible preferred stock	—	203
Plus: Dividends accrued on redeemable convertible preferred stock	—	(1,553)
Adjusted net loss attributable to common stockholders	$ (8,473)	$ (6,152)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	17,834,570	444,132
Basic and diluted net loss per common share outstanding	$ (0.48)	$ (13.85)

Accretion and dividends included in the table above were calculated through the IPO date.

The Company's potential dilutive securities, which include stock options and redeemable convertible preferred stock, have been excluded from the computation of diluted net loss per share attributable to common stockholders whenever the effect of including them would be to reduce the net loss per share. In periods where there is a net loss, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The following potential common shares, presented based on shares outstanding as of March 31, 2020 and 2019, were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Shares as of March 31,	
	2020	2019
Series A redeemable convertible preferred stock	—	15,387,923
Series B redeemable convertible preferred stock	—	22,608,695
Series C redeemable convertible preferred stock	—	44,946,987
Outstanding stock options	2,205,535	1,059,057
	2,205,535	84,002,662

11. Collaborative and Licensing Agreements

The Company enters into collaborative and licensing agreements with pharmaceutical companies to in-license, develop, manufacture and/or market products that fit within its business strategy.

Endo Pharmaceuticals Inc.

In May 2011, the Company entered into an agreement with Penwest Pharmaceuticals Co. ("Penwest") (subsequently merged into its parent, Endo Pharmaceuticals Inc. ("Endo")) for an exclusive worldwide sublicensable license under certain patent rights and know-how controlled by Penwest to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including an extended release formulation such as nalbuphine ER, in all fields and for any use.

Under the license agreement, the Company paid Penwest a non-creditable, non-refundable upfront license fee of $25. The Company may also become obligated to make milestone payments to Endo of $250, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate, such as the PRISM trial, and $750, which would become due upon the marketing approval of a licensed product in the United States, and to pay mid-single-digit royalties based on net sales of the licensed products by the Company, its affiliates and sublicensees. In addition, the Company is obligated to pay Endo a low-to-mid double-digit percentage of certain income it receives from sublicensees, based on the date of the definitive agreement under which the sublicense was granted.

The Company's royalty obligation with respect to each licensed product in each country commences upon the first commercial sale of the product in that country and extends until the later of the expiration, unenforceability or invalidation of the last valid claim of any licensed patent or application covering the licensed product in the country or the expiration of 10 years after the first commercial sale of the licensed product in the country, which period is referred to as the royalty term. Upon the expiration of the royalty term for a product in a country, the Company is thereafter obligated to pay a low single-digit know-how and trademark royalty.

Under the agreement, the Company has granted Endo a non-exclusive, royalty-free (except for pass-through payments to third parties), sublicensable license under its relevant patent rights, to use any improvement the Company makes to Endo's controlled release technology, for any product other than the products under which it is licensed by Endo.

Both the Company and Endo have the right to terminate the agreement if the other party materially breaches the agreement and fails to cure the breach within specified cure periods. Endo also has the right to terminate in the event the Company undergoes specified bankruptcy, insolvency or liquidation events, and the Company has the right to terminate the agreement at its convenience at any time on 180 days' notice to Endo. Additionally, if the Company or any of the Company's sublicensees challenge the validity or enforceability of any licensed patent rights covering a licensed product, and that challenge is not terminated within a specified period, the agreement will immediately terminate and all licenses granted under the agreement shall be revoked.

Upon termination of the agreement, the Company must transfer to Endo all regulatory filings and approvals relating to the development, manufacture or commercialization of the licensed products and all trademarks, other than the Company's corporate trademarks, then being used in connection with the licensed products. If the agreement is terminated under certain specified circumstances, the Company will be deemed to have granted Endo a perpetual, royalty-free (except for pass-through payments to third parties), worldwide, exclusive, sublicensable license, under any improvements the Company made to the licensed know-how, and any related patent rights the Company has, to manufacture and commercialize the licensed products.

Exclusive License Agreement with Rutgers

On November 6, 2018, the Company entered into an agreement with Rutgers, The State University of New Jersey ("Rutgers") for an exclusive, worldwide, sublicensable license under certain patent rights controlled by Rutgers and for a non-exclusive, worldwide, sublicensable license under certain know-how controlled by Rutgers, in each case to develop and commercialize products incorporating nalbuphine for any human or animal use.

Upon entering into the license agreement, the Company paid Rutgers a minimal upfront license issue fee, which was recorded as R&D expense in 2018 and agreed to pay Rutgers a minimal annual license fee. The Company may become obligated to make milestone payments to Rutgers in the aggregate of up to $331 based on the achievement of certain clinical, regulatory and sales milestones. The Company has also agreed to pay Rutgers a low single-digit percentage of certain income it receives from sublicensees and to pay tiered low single-digit royalties based on net sales of licensed products by the Company and its affiliates and sublicensees.

The Company's royalty obligation with respect to each licensed product in each country commences on the date of the first commercial sale of the licensed product in that country following receipt of marketing approval and extends until the later of the date of expiration, unenforceability or invalidation of the last valid claim of any licensed patent or patent application covering the licensed product in the country and 10 years after the first commercial sale of the first licensed product sold anywhere in the world, which period is referred to as the royalty term. Upon the expiration of the royalty term for a licensed product in a country, the license granted to the Company under the agreement shall become perpetual, fully paid-up, irrevocable and royalty-free in such country. The royalty is subject to reduction in certain circumstances.

Restructuring Agreement with MentiNova, LLC

On November 6, 2018, concurrent with the signing of the agreement with Rutgers described above, the Company entered into a restructuring agreement with MentiNova, LLC ("MentiNova") for the purchase of specified information and know-how, specified contractual rights and benefits, and all books and records of MentiNova related thereto (collectively, the "Acquired Assets").

Upon entering into the license agreement, the Company paid MentiNova an aggregate upfront payment of $119, which was recorded as R&D expense in 2018, subject to specified closing adjustments. The Company may become obligated to make milestone payments to MentiNova in the aggregate of up to $1,188 based on the achievement of certain clinical and regulatory milestones as well as tiered low single-digit royalties based on net sales of products containing nalbuphine as the sole active pharmaceutical ingredient that are developed by the Company using the Acquired Assets or the intellectual property licensed to the Company under the Rutgers agreement described above (the "Rutgers IP") for indications that are within the scope of the Rutgers IP. The royalty is subject to reduction in certain circumstances.

12. Commitments and Contingencies

A significant portion of the Company's development activities are outsourced to third parties under agreements, including with clinical research organizations, and contract manufacturers in connection with the production of clinical trial materials. These arrangements may require the Company to pay termination costs to the third parties for reimbursement of costs and expenses incurred in the event of the orderly termination of contractual services.

The Company also has commitments under lease and licensing agreements *(Note 4 and Note 11)*.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our condensed consolidated financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q and our audited consolidated financial statements and related notes for the year ended December 31, 2019 included in our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the Securities and Exchange Commission, or SEC, on March 16, 2020. Some of the statements contained in this discussion and analysis or set forth elsewhere in this Quarterly Report on Form 10-Q, including information with respect to our plans and strategy for our business, constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," "could," "continue" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We have based these forward-looking statements on our current expectations and projections about future events. The following information and any forward-looking statements should be considered in light of factors discussed elsewhere in this Quarterly Report on Form 10-Q, particularly including those risks identified in Part II-Item 1A "Risk Factors" and our other filings with the SEC.

Our actual results and timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Quarterly Report on Form 10-Q. Statements made herein are as of the date of the filing of this Quarterly Report on Form 10-Q with the SEC and should not be relied upon as of any subsequent date. Even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Quarterly Report on Form 10-Q, they may not be predictive of results or developments in future periods. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of nalbuphine ER to treat serious neurologically mediated conditions. We are developing nalbuphine ER for the treatment of chronic pruritus, chronic cough in patients with idiopathic pulmonary fibrosis, or IPF, and levodopa-induced dyskinesia, or LID, in patients with Parkinson's disease.

We are conducting a Phase 2b/3 clinical trial of nalbuphine ER, which we refer to as the PRISM trial, in patients with severe pruritus associated with prurigo nodularis. The PRISM trial is a randomized, double-blind, placebo controlled, two-arm treatment study that is designed to evaluate the safety and anti-pruritic efficacy of nalbuphine ER in approximately 240 patients in the United States and Europe. The pace of enrollment in the trial has been impacted by the COVID-19 pandemic with new patient screening and most patient enrollment temporarily halted. Patient screening restrictions have been lifted in the United States and are in the process of being lifted in Europe. We expect many of our sites will restart patient screening and enrollment throughout May and June 2020. The protocol for the PRISM trial provides for a sample size re-estimation, or SSRE, analysis once approximately 50% of the patients in the trial are evaluable for the primary endpoint. In light of the pandemic-related delays, we have decided to conduct the SSRE analysis once approximately 45% of the patients in the trial are evaluable for the primary endpoint. We have enrolled all the patients that will be included in the SSRE and will conduct the SSRE analysis once the last of these patients has completed the 14-week blinded treatment period. We expect the SSRE analysis will occur in mid-2020. We plan to provide updated guidance on our expected timing to report top-line data from the 14-week blinded treatment period of the PRISM trial when we report the results of the SSRE analysis in mid-2020 based on the results of the SSRE analysis and our progress in restarting patient screening and enrollment related to COVID-19.

We are also conducting a Phase 2 clinical trial of nalbuphine ER for chronic cough in patients with IPF. This Phase 2 clinical trial is a randomized, double-blind, placebo controlled, two-treatment, two-period, crossover study designed to evaluate the efficacy, safety, tolerability and dosing of nalbuphine ER for chronic cough in up to 56 patients with IPF in the United Kingdom. Due to the COVID-19 pandemic and the specific at-risk nature of IPF patients our clinical sites halted their enrollment and treatment of patients in this trial. We believe that enrollment may restart in the second half of 2020 and plan to provide guidance on the expected timing of top-line data from the trial in the second half of 2020.

In addition, we are conducting a Phase 1b clinical trial in patients with chronic liver disease to evaluate the safety and pharmacokinetics, or PK, of nalbuphine ER in this population. This trial was designed as an open label, non-randomized, parallel-group, single and multiple ascending dose pharmacokinetic trial in patients with mild, moderate and severe hepatic impairment. We completed the single ascending dosing portion of this trial in patients with mild and moderate hepatic impairment and there were no serious adverse events reported in the trial. After reviewing the safety and PK data generated to date in the single ascending dose portion of the trial, we believe that these data are sufficient to support further investigation of nalbuphine ER in potential future safety and efficacy studies in patients with relevant liver diseases. We intend to start planning for a Phase 2 trial of nalbuphine ER in patients with pruritus associated with primary biliary cholangitis, or PBC. In addition, we intend to use the data from the hepatic impairment study to support a new drug application, or NDA, submission for nalbuphine ER for pruritus in prurigo nodularis.

We have written the protocol for a Phase 2 clinical trial for LID in patients with Parkinson's disease and plan to submit an Investigational New Drug, or IND, application to the FDA in the upcoming months.

We are currently focusing our resources on completing the PRISM trial and Phase 2 trial for chronic cough in patients with IPF. We are continuing to prepare to conduct the Phase 2 trials for LID in patients with Parkinson's disease and pruritus associated with PBC but plan to prioritize our cash and operational resources on our two lead clinical programs.

Since commencing operations in 2011, we have devoted substantially all of our efforts and financial resources to the clinical development of nalbuphine ER. We have not generated any revenue from product sales and, as a result, we have never been profitable and have incurred net losses in each year since commencement of our operations. As of March 31, 2020, we had an accumulated deficit of $122.7 million, primarily as a result of research and development and general and administrative expenses. We do not expect to generate product revenue unless and until we obtain marketing approval for and commercialize nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, chronic cough in patients with IPF or LID in patients with Parkinson's disease, and we can provide no assurance that we will ever generate significant revenue or profits.

On May 9, 2019, we issued and sold 5,500,000 shares of common stock in our initial public offering, or IPO, and 1,500,000 shares of common stock in a concurrent private placement, in each case at an offering price of $10.00 per share, for combined net proceeds of $62.1 million after deducting aggregate underwriting discounts and commissions and private placement agent fees of $4.9 million and other offering expenses of $3.0 million. Upon the closing of the IPO, our preferred stock then outstanding converted into an aggregate of 10,381,234 shares of common stock.

As of March 31, 2020, we had cash and cash equivalents of $52.6 million. We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2021. Our estimate as to how long we expect our existing cash and cash equivalents to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we expect. See "—Liquidity and Capital Resources." Our future viability beyond that point is dependent on our ability to raise additional capital to finance our operations.

We expect to incur substantial expenditures in the foreseeable future as we advance nalbuphine ER through clinical development, the regulatory approval process and, if approved, commercial launch activities. Specifically, in the near term, we expect to incur substantial expenses relating to our ongoing Phase 2b/3 PRISM trial in patients with pruritus associated with prurigo nodularis, the additional Phase 3 clinical trial we will be required to conduct to support the submission of an NDA to the United States Food and Drug Administration, or FDA, for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, our ongoing Phase 2 clinical trial in chronic cough in patients with IPF, the development and validation of our commercial manufacturing process for nalbuphine ER and other development activities, including potentially commencing Phase 2 clinical trials for the treatment of LID in patients with Parkinson's disease and for pruritus associated with PBC. In addition, we may incur additional expenses as a result of COVID-19 and resulting clinical trial delays and interruptions. Furthermore, we expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company.

We will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from sales of nalbuphine ER, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, including potential collaborations with other companies or other strategic transactions. Adequate funding may not be available to us on acceptable terms, or at all. If we fail to raise capital or enter into such agreements as and when needed, we may have to significantly delay, scale back or discontinue the development and commercialization of nalbuphine ER for one or more indications or delay our efforts to expand our product pipeline.

Components of Operating Results

Operating Expenses

Research and Development Expenses

All of our research and development expenses consist of expenses incurred in connection with the development of nalbuphine ER. These expenses include certain payroll and personnel expenses, including stock-based compensation, consulting costs, contract manufacturing costs and fees paid to clinical research organizations, or CROs, to conduct certain research and development activities on our behalf. We do not allocate our costs by each indication for which we are developing nalbuphine ER, as a significant amount of our development activities broadly support all indications. In addition, several of our departments support our nalbuphine ER drug candidate development program and we do not identify internal costs for each potential indication.

We expect our research and development expenses to increase over the next few years as we pursue our development program, pursue regulatory approval of nalbuphine ER in the United States and Europe and prepare for a possible commercial launch of nalbuphine ER. Predicting the timing or the cost to conduct our nalbuphine ER development program and prepare for a possible commercial launch of nalbuphine ER is difficult and delays may occur because of many factors including factors outside of our control such as the sample size re-estimation for our PRISM trial. For example, if the FDA or other regulatory authorities were to require us to conduct clinical trials beyond those that we currently anticipate, or if we experience significant delays in enrollment, whether as a result of the COVID-19 pandemic or otherwise, in any of our clinical trials, we could be required to expend significant additional financial resources and time on our development program. Furthermore, we are unable to predict when or if nalbuphine ER will receive regulatory approval in the United States or elsewhere with any certainty.

General and Administrative Expenses

General and administrative expenses consist principally of personnel-related costs, including stock-based compensation, for personnel in executive, finance, commercial and other administrative functions, professional fees for legal, consulting and accounting services as well as rent and other general operating expenses not otherwise classified as research and development expenses.

We anticipate that our general and administrative expenses will increase as a result of increased personnel costs, including stock-based compensation, expanded infrastructure and higher consulting, legal and accounting services associated with maintaining compliance with stock exchange listing and SEC requirements, investor relations costs and director and officer insurance premiums associated with being a public company.

Other Income (Expense), Net

Change in Fair Value of Obligation for Loan Success Fee

In connection with the Term Loan, we entered into the Success Fee Agreement under which we agreed to pay the lenders a Success Fee upon the occurrence of an exit event, as defined in the Success Fee Agreement. We recognized changes in the fair value of this obligation for the Success Fee in our statements of operations as a component of other income (expense), net. We recognized changes in the fair value of the obligation for the Success Fee until the Success Fee payment was triggered and paid upon the closing of our IPO in May 2019.

Interest Income

Interest income consists of interest earned from money market funds on our cash and cash equivalents.

Results of Operations

Comparison of the Three Months Ended March 31, 2020 and 2019

The following table summarizes our results of operations for the periods indicated (in thousands):

	Three Months Ended March 31,		
	2020	2019	Change
Operating expenses:			
Research and development	$ 6,019	$ 3,338	$ 2,681
General and administrative	2,620	1,474	1,146
Total operating expenses	8,639	4,812	3,827
Loss from operations	(8,639)	(4,812)	(3,827)
Other income (expense):			
Change in fair value of obligation for loan success fee	—	(52)	52
Interest income	157	58	99
Total other income (expense), net	157	6	151
Loss before income tax benefit	(8,482)	(4,806)	(3,676)
Income tax benefit	9	4	5
Net loss	$ (8,473)	$ (4,802)	$ (3,671)

Operating Expenses

Research and Development Expenses

The following table summarizes our research and development expenses for the periods indicated (in thousands):

	Three Months Ended March 31,	
	2020	2019
Clinical development expenses	$ 4,956	$ 2,500
Personnel and related expenses	694	589
Consulting expenses and professional fees	234	157
Stock-based compensation expenses	93	22
Other research and development expenses	42	70
Total research and development expenses	$ 6,019	$ 3,338

Research and development expenses for the three months ended March 31, 2020 increased to $6.0 million from $3.3 million for the corresponding period in 2019. The increase was primarily due to a $2.5 million increase in clinical development expenses primarily related to increased activity in our Phase 2b/3 PRISM trial and our Phase 2 trial in chronic cough in patients with IPF as well as an increase in expenses related to the purchase of clinical trial supplies. In addition, personnel and related expenses increased by $0.2 million as a result of an increase in our employee headcount. For the periods presented, all of our research and development expenses related to our development activity for nalbuphine ER.

General and Administrative Expenses

General and administrative expenses for the three months ended March 31, 2020 increased to $2.6 million from $1.5 million for the corresponding period in 2019. The increase was primarily due to an increase in stock-based compensation expenses of $0.6 million, which we incurred from the issuance of new stock option grants in the second quarter of 2019 upon the IPO and in the first quarter of 2020, an increase in expenses related to being a public company of $0.4 million and an increase in consulting expenses and professional fees of $0.2 million.

Other Income (Expense), Net

Other income (expense), net for the three months ended March 31, 2020 increased to other income, net of $0.2 million from other income, net of $6 thousand for the corresponding period in 2019. The increase reflects the increased interest income of $0.2 million in the three months ended March 31, 2020 due to our larger cash balance following our IPO in May 2019.

Liquidity and Capital Resources

Since our inception, we have not generated any revenue and have incurred significant operating losses and negative cash flows from our operations. Prior to the completion of our IPO and concurrent private placement in May 2019, we financed our operations primarily through private placements of our preferred stock and convertible notes as well as borrowings under a term loan facility. From inception to our IPO, we raised an aggregate of $102.2 million in gross proceeds from sales of our preferred stock and convertible notes and borrowed $15.0 million under the term loan facility. As of June 30, 2018, all amounts owed under the term loan facility had been paid in full.

In May 2019, we issued and sold 5,500,000 shares of common stock in our IPO and 1,500,000 shares of common stock in a concurrent private placement, in each case at an offering price of $10.00 per share, for combined net proceeds of $62.1 million after deducting aggregate underwriting discounts and commissions and private placement agent fees of $4.9 million and other offering expenses of $3.0 million.

As of March 31, 2020, we had cash and cash equivalents of $52.6 million. Our cash and cash equivalents are primarily held in money market accounts.

Cash Flows

The following table summarizes our cash flows for each of the periods presented below (in thousands):

	Three Months Ended March 31,	
	2020	2019
Net cash used in operating activities	$ (4,673)	$ (4,096)
Net cash used in investing activities	—	(9)
Net cash provided by financing activities	—	9,849
Net cash increase (decrease)	$ (4,673)	$ 5,744

Operating Activities

During the three months ended March 31, 2020, operating activities used $4.7 million of cash, resulting from our net loss of $8.5 million, partially offset by changes in our operating assets and liabilities of $3.1 million and non-cash charges of $0.7 million. Changes in our operating assets and liabilities for the three months ended March 31, 2020 consisted of a $1.4 million increase in accrued expenses, a $0.6 million increase in accounts payable, a $0.6 million decrease in prepaid expenses and a $0.4 million decrease in receivables. The increase in accrued expenses was primarily due to increases in accruals related to our Phase 2b/3 PRISM trial in prurigo nodularis and our Phase 2 trial for chronic cough in IPF. The increase in accounts payable was primarily due to timing of vendor invoices. The decrease in prepaid expenses was primarily due to a decrease in prepayments of our insurance and a decrease of prepayments under our ongoing research, development and clinical trial work performed by CROs. The decrease in receivables was primarily due to prepayments made to one of our vendors, which we received in the first quarter of 2020. The non-cash charges for three months ended March 31, 2020 consisted primarily of stock-based compensation expense of $0.7 million.

During the three months ended March 31, 2019, operating activities used $4.1 million of cash, resulting from our net loss of $4.8 million, partially offset by net cash provided by changes in our operating assets and liabilities of $0.5 million and non-cash charges of $0.2 million. Net cash provided by changes in our operating assets and liabilities for the three months ended March 31, 2019 consisted primarily of a $0.9 million increase in accrued expenses which was primarily due to increases in accruals related to our Phase 2b/3 PRISM trial in prurigo nodularis. The non-cash charges for the three months ended March 31, 2019 consisted primarily of stock-based compensation expense of $0.1 million.

Investing Activities

During the three months ended March 31, 2020 no cash was used in investing activities.

During the three months ended March 31, 2019, we used an insignificant amount of cash in investing activities, consisting of purchases of property and equipment.

Financing Activities

During the three months ended March 31, 2020, no cash was provided by financing activities.

During the three months ended March 31, 2019, net cash provided by financing activities was $9.8 million, primarily consisting of net cash proceeds of $10.0 million from our sales of shares of Series C preferred stock in the third tranche of our Series C preferred stock financing in January 2019, partially offset by deferred costs relating to our IPO of $0.1 million.

Funding Requirements

We expect to incur substantial expenditures in the foreseeable future as we advance nalbuphine ER through clinical development, the regulatory approval process and, if approved, commercial launch activities. Specifically, in the near term, we expect to incur substantial expenses relating to our ongoing Phase 2b/3 PRISM trial, the additional Phase 3 clinical trial we will need to conduct to support the submission of an NDA to the FDA and a marketing authorization application to the European Medicines Agency for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, our ongoing Phase 2 clinical trial in chronic cough in patients with IPF, the costs of commercialization activities, including manufacturing capabilities, for nalbuphine ER and other development activities including potentially commencing Phase 2 clinical trials for the treatment of LID in patients with Parkinson's disease and for pruritus associated with PBC. In addition, we may incur additional expenses as a result of COVID-19 and resulting clinical trial delays and interruptions. Furthermore, we expect to continue to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company.

We will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from sales of nalbuphine ER, if ever, we expect to finance our operations through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, including the results of the sample size re-estimation analysis for our ongoing Phase 2b/3 PRISM trial that we expect will take place in mid-2020 as well as the scope, progress, timing, costs and results of clinical trials of nalbuphine ER for other serious neurologically mediated conditions, including our ongoing Phase 2 trial for chronic cough in patients with IPF, as well as any future product candidates;
- the impact of the COVID-19 pandemic on the scope, progress, timing, costs and results of our ongoing and planned clinical trials of nalbuphine ER;
- the number and characteristics of indications for which we seek to develop nalbuphine ER or any future product candidates, and their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs of supportive clinical studies such as our planned human abuse liability study and our planned Thorough QT studies;
- the costs associated with the manufacture of necessary quantities of nalbuphine ER or any future product candidate for clinical development in connection with regulatory submissions;
- the costs of commercialization activities for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or for any future product candidates that receive marketing approval, if any, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approvals, revenue, if any, received from commercial sales of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or from any future product candidates;
- our ability to identify potential collaborators for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any future product candidates and the terms and timing of any collaboration agreement that we may establish for the development and any commercialization of such product candidates;
- the extent to which we acquire or in-license rights to other potential product candidates or technologies, and the terms and timing of any such acquisition or licensing arrangements;
- our headcount growth and associated costs as we expand our research and development activities and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining, expanding and protecting our intellectual property rights and defending against intellectual property-related claims;
- the effect of competing technological and market developments;

- our ability to establish and maintain healthcare coverage and adequate reimbursement for our products; and
- the costs of operating as a public company.

We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2021.

We have based our estimates as to how long we expect we will be able to fund our operations on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect, in which case we would be required to obtain additional financing, which may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We do not have any committed external source of funds. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to complete the clinical development and commercialization of nalbuphine ER for pruritus associated with prurigo nodularis or any other indication. If we raise additional funds by issuing equity securities, our stockholders may experience dilution. Any future debt financing into which we enter would result in fixed payment obligations and may involve agreements that include grants of security interests on our assets and restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, granting liens over our assets, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. Any debt financing or additional equity that we raise may contain terms that could adversely affect our common stockholders.

If we are unable to raise sufficient capital as and when needed, we may be required to delay, reduce or abandon our product development programs or commercialization efforts. If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to future revenue streams or product candidates or grant licenses on terms that may not be favorable to us.

Critical Accounting Policies and Use of Estimates

Our financial statements have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these 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 the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our 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 readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

During the three months ended March 31, 2020, there were no material changes to our critical accounting policies. Our critical accounting policies are described in the notes to the consolidated financial statements and under the heading “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Use of Estimates” in our 2019 Annual Report on Form 10-K for the year ended December 31, 2019, and in the notes to the condensed consolidated financial statements appearing elsewhere in this Quarterly Report on Form 10-Q.

Off-Balance Sheet Arrangements

Since our inception, we have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC. See Note 12 to our condensed consolidated financial statements included elsewhere in this Quarterly Report on Form 10-Q for discussion regarding our commitments and contingent commitments.

Recently Adopted Accounting Pronouncements

There have been no new accounting pronouncements adopted during the three months ended March 31, 2020.

Recently Issued Accounting Pronouncements

There have been no new accounting pronouncements during the three months ended March 31, 2020, as compared to the recent accounting pronouncements described in Note 2 to our audited consolidated financial statements for the year ended December 31, 2019 included in our Annual Report on Form 10-K for the year ended December 31, 2019, which could be expected to materially impact our unaudited condensed consolidated financial statements.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

Not Required.

Item 4. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), as of March 31, 2020. Our disclosure controls and procedures are designed to ensure that information we are required to disclose in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate to allow timely decisions regarding required disclosures, and is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of March 31, 2020, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended March 31, 2020 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II—OTHER INFORMATION

Item 1. Legal Proceedings.

We are not subject to any material legal proceedings.

Item 1A. Risk Factors.

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

Risks Related to Our Business Operations

We face risks related to health epidemics and other widespread outbreaks of contagious disease, including the novel coronavirus pandemic, or COVID-19, which has delayed our ability to complete our ongoing clinical trials, disrupted our business operations and may further delay our clinical trials, interrupt our supply chain, disrupt regulatory activities, or have other adverse effects on our business and operations. In addition, this pandemic has caused substantial disruption in the financial markets and economies worldwide, which could result in adverse effects on our business and operations.

Significant outbreaks of contagious diseases, and other adverse public health developments, could have a material impact on our business operations and operating results. In December 2019, an outbreak of respiratory illness caused by a strain of novel coronavirus, COVID-19, began in China. That outbreak has led to millions of confirmed cases worldwide, including in the United States and other countries where we are conducting clinical trials or activities in support thereof. The World Health Organization declared the outbreak a global public health emergency on January 30, 2020 and declared it a pandemic on March 11, 2020. In addition to those who have been directly affected, billions more have been affected by governmental efforts around the world to slow the spread of the outbreak.

The outbreak and government measures taken in response thereto have also had a significant impact, both direct and indirect, on segments of the global economy and have interrupted our clinical trial activities, disrupted our business operations and have the potential to interrupt our supply chain. We have experienced restrictions and delays at our existing clinical sites and delays in activating new clinical sites. For example, in our ongoing Phase 2b/3 trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, which we refer to as our PRISM trial, new patient screening and most enrollment has been temporarily halted due to the COVID-19 pandemic, which will delay our ability to report top-line data for that trial. In addition, the clinical sites in our ongoing Phase 2 trial for chronic cough in patients with idiopathic pulmonary fibrosis, or IPF, have suspended enrollment and treatment of patients in the trial due to the vulnerability of IPF patients to COVID-19. Furthermore, multiple sites in both trials have begun requiring remote monitoring of patient data. The COVID-19 pandemic may also adversely affect our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, and may result in further disruptions to our clinical trials due to prioritization of hospital and medical resources toward the outbreak, restrictions on travel of patients and healthcare providers, potential unwillingness of patients to enroll in trials at this time, or the inability of patients to comply with clinical trial protocols if quarantines or travel restrictions impede patient movement or interrupt healthcare services. The response to the COVID-19 pandemic may also redirect resources of regulators in a way that could adversely impact our ability to progress regulatory approvals and we may face impediments to regulatory meetings and approvals relating to our clinical trials due to measures intended to limit in-person interactions.

COVID-19 may also affect employees of third-party contract research organizations located in affected geographies that we rely upon to carry out our clinical trials. The spread of COVID-19, or another infectious disease, could also negatively affect the operations at our third-party suppliers, which could result in delays or disruptions in the supply of drug product used in our clinical trials. In addition, we have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees, including temporarily requiring all employees to work remotely, suspending all non-essential travel worldwide for our employees and discouraging employee attendance at industry events and in-person work-related meetings, which could negatively affect our business.

We cannot presently predict the scope and severity of the disruptions we may continue to experience as a result of the COVID-19 pandemic. If we or any of the third parties with whom we engage experience further business disruptions that are greater than we or they anticipate, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively affected. Additionally, the pandemic has already caused significant disruptions in the financial markets, and may continue to cause such disruptions, which could impact our ability to raise additional funds and has also impacted, and may continue to impact, the volatility of our stock price and trading in our stock.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur significant and increasing losses for the foreseeable future, and may never achieve or maintain profitability.

We have incurred significant annual net losses every year since our inception. We expect to continue to incur significant and increasing net losses for at least the next several years. Our net losses were $8.5 million, $26.1 million and $20.5 million for the three months ended March 31, 2020 and the years ended December 31, 2019 and 2018, respectively. As of March 31, 2020, we had an accumulated deficit of $122.7 million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through our initial public offering and private placements of our convertible preferred stock prior to our initial public offering. We have devoted substantially all of our financial resources and efforts to the clinical development of our product candidate nalbuphine ER and related activities. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue to develop and conduct clinical trials of nalbuphine ER, including our ongoing Phase 2b/3 trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, which we refer to as our PRISM trial, and our other ongoing clinical trials of nalbuphine ER in other serious neurologically mediated conditions, including our Phase 2 trial for chronic cough in patients with IPF;
- significantly increase the number of patients in the PRISM trial to the extent required by the sample size re-estimation, or SSRE, analysis;
- complete other development work required for the filing of a new drug application, or NDA, with the U.S. Food and Drug Administration, or FDA, and the filing of a marketing authorization application, or MAA, with the European Medicines Agency, or EMA, for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, including completing our PRISM trial and at least one additional Phase 3 clinical trial in this indication;
- seek regulatory and marketing approvals for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for other serious neurologically mediated conditions or for any future product candidate that successfully completes clinical trials, if any;
- complete any post-approval commitments, including a pediatric development plan;
- establish sales, marketing, distribution and other commercial infrastructure to commercialize any products for which we may obtain marketing approval;
- require the manufacture of larger quantities of nalbuphine ER or any future product candidate for clinical development and, potentially, commercialization;
- acquire or in-license rights to other potential product candidates or technologies;
- initiate and conduct research, preclinical and clinical development efforts for any future product candidates;
- maintain, expand and protect our intellectual property portfolio;
- hire and retain additional personnel, such as clinical, regulatory and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts, and to help us comply with our obligations as a public company; and
- add equipment and physical infrastructure to support our development program for nalbuphine ER and for any future product candidates.

In addition, we may incur additional expenses as a result of COVID-19 and resulting clinical trial delays and interruptions. Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for, and successfully commercialize, nalbuphine ER or any future product candidate. Successful commercialization will require achievement of key milestones, including completing clinical trials of nalbuphine ER or any future product candidate, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for any such product from private insurance or government payors. For example, in order to successfully commercialize nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, we will be required, at a minimum, to

successfully complete our ongoing PRISM trial as well as an additional Phase 3 clinical trial prior to submitting an NDA and MAA to regulatory authorities to obtain marketing approval. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We may never succeed in these activities and, even if we do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our development efforts, develop a pipeline of product candidates or continue our operations.

We have a limited operating history and no products approved for commercial sale, which may make it difficult to evaluate the prospects for our future success and viability.

We were founded and commenced operations in 2011. Our operations to date have been limited to financing and staffing our company and conducting preclinical and clinical development of nalbuphine ER. We have not yet demonstrated an ability to successfully complete clinical development of any product candidates, obtain marketing approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization of any products. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by clinical-stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. If we are able to obtain marketing approval for nalbuphine ER or any future product candidate, we will need to transition from a company focused on clinical development to a company capable of supporting commercial activities. We may not be successful in effectuating such a transition.

We expect our financial condition and operating results will 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 quarterly or annual periods as indications of future operating performance.

We will need substantial additional funding, and if we are unable to raise sufficient capital when needed on acceptable terms, or at all, we could be forced to delay, reduce or abandon our product development programs or commercialization efforts.

Developing pharmaceutical products, including conducting preclinical and nonclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. We have consumed substantial amounts of cash since our inception. For example, in the three months ended March 31, 2020 and in the years ended December 31, 2019 and 2018, we used net cash of $4.7, $23.1 million and $18.3 million, respectively, in our operating activities, substantially all of which related to development activities for nalbuphine ER. As of March 31, 2020, our cash and cash equivalents were $52.6 million. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we continue to develop and conduct clinical trials of nalbuphine ER, including our ongoing PRISM trial and the additional Phase 3 clinical trial we will need to conduct for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and our other ongoing clinical trials, acquire or in-license rights to other potential product candidates or technologies and seek regulatory and marketing approvals for nalbuphine ER or any future product candidate that successfully completes clinical trials, if any. In addition, we may incur additional expenses as a result of COVID-19 and resulting clinical trial delays and interruptions. In addition, if we obtain marketing approval for nalbuphine ER or any future product candidate, we may incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. For instance, we currently intend to commercialize nalbuphine ER in the United States ourselves by developing a focused, specialty sales, marketing and distribution organization. Furthermore, we expect to incur significant additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise sufficient capital when needed on acceptable terms, or at all, we may be forced to delay, reduce or abandon our development programs or any future commercialization efforts.

We plan to use our existing cash and cash equivalents to fund the development of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and the treatment of chronic cough in patients with IPF, to fund the development of nalbuphine ER for other serious neurologically mediated conditions and for working capital and other general corporate purposes. We will be required to expend significant funds in order to advance the development of nalbuphine ER in multiple indications, as well as any future product candidates we may seek to develop. Our existing cash and cash equivalents will not be sufficient to complete development of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other condition or of any future product candidate. We do not have any committed external source of funds. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2021. Our estimate as to how long we expect our existing cash and cash equivalents to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, including the results of the sample size re-estimation analysis for our ongoing Phase 2b/3 PRISM trial that we expect will take place in mid-2020 as well as the scope, progress, timing, costs and results of clinical trials of nalbuphine ER for other serious neurologically mediated conditions, including our ongoing Phase 2 trial for chronic cough in patients with IPF, as well as any future product candidates;
- the impacts of the COVID-19 pandemic on the scope, progress, timing, costs and results of our ongoing and planned clinical trials of nalbuphine ER;
- the number and characteristics of indications for which we seek to develop nalbuphine ER or any future product candidates, and their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs of supportive clinical studies such as our planned human abuse liability, or HAL, study and our planned Thorough QT, or TQT, studies;
- the costs associated with the manufacture of necessary quantities of nalbuphine ER or any future product candidate for clinical development in connection with regulatory submissions;
- the costs of commercialization activities for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or for any future product candidates that receive marketing approval, if any, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approvals, revenue, if any, received from commercial sales of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or from any future product candidates;
- our ability to identify potential collaborators for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any future product candidates and the terms and timing of any collaboration agreement that we may establish for the development and any commercialization of such product candidates;
- the extent to which we acquire or in-license rights to other potential product candidates or technologies, and the terms and timing of any such acquisition or licensing arrangements;
- our headcount growth and associated costs as we expand our research and development activities and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining, expanding and protecting our intellectual property rights and defending against intellectual property-related claims;
- the effect of competing technologies and market developments;
- our ability to establish and maintain healthcare coverage and adequate reimbursement for our products; and
- the costs of operating as a public company.

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

We expect our expenses to increase substantially in connection with our planned operations, particularly as we conduct our ongoing PRISM trial and our other ongoing clinical trials as well as the additional Phase 3 clinical trial we will need to conduct for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and develop nalbuphine ER for the treatment of other serious neurologically mediated conditions. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, your ownership interest may be diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect your rights as a common stockholder. In addition, debt financing, if available, would result in fixed payment obligations and may involve agreements that include grants of security interests on our assets and restrictive covenants that limit our ability to take specific actions, such as incurring additional debt,

making capital expenditures, granting liens over our assets, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. Securing financing could also require a substantial amount of time from our management and may divert a disproportionate amount of their attention away from daily activities, which may adversely affect our management's ability to oversee the development of nalbuphine ER or that of any future product candidates. If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to future revenue streams or product candidates or grant licenses on terms that may not be favorable to us.

Risks Related to the Development and Commercialization of Nalbuphine ER and Any Future Product Candidates

We are dependent on the successful development and commercialization of nalbuphine ER, our sole product candidate. If we are unable to complete the clinical development of, obtain marketing approval for or successfully commercialize nalbuphine ER, or if we experience significant delays in doing so, our business would be substantially harmed.

We currently have no products approved for sale and are investing substantially all of our efforts and financial resources to fund the development of nalbuphine ER for multiple serious neurologically mediated conditions. Our prospects are dependent on our ability to develop, obtain marketing approval for and successfully commercialize nalbuphine ER in one or more indications as we currently have no other product candidates under development. We may acquire or in-license rights to other potential product candidates or technologies in the future, but we are currently not developing any other product candidates.

Our most advanced program for nalbuphine ER is our program to develop nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, as our efforts to develop nalbuphine ER for other serious neurologically mediated conditions are only at an early stage. As a result, if our efforts to develop and commercialize nalbuphine ER for the treatment of pruritus associated with prurigo nodularis are unsuccessful, or we experience significant delays in doing so, our business could also be substantially harmed.

The success of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, as well as for other serious neurologically mediated conditions, will depend on several factors, including the following:

- successfully recruiting, enrolling and retaining patients in and completing our PRISM trial;
- initiating and successfully recruiting, enrolling and retaining patients in and completing additional clinical and nonclinical trials, including the additional Phase 3 clinical trial we will need to conduct for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and other supportive clinical studies such as our planned HAL study and TQT studies;
- demonstrating safety, tolerability and efficacy profiles that are satisfactory to the FDA, EMA and other comparable regulatory authorities for marketing approval;
- receiving timely marketing approvals from applicable regulatory authorities;
- managing the extent and cost of any required post-marketing approval commitments to applicable regulatory authorities;
- establishing and maintaining arrangements with our third-party supplier of drug substance for nalbuphine ER;
- establishing and maintaining arrangements with third-party manufacturers of nalbuphine ER, including developing, validating and maintaining a commercially viable manufacturing process that is compliant with current good manufacturing practices, or cGMPs;
- obtaining, maintaining and protecting our patents, trade secrets and regulatory exclusivity in the United States and other countries;
- establishing a focused, specialty sales organization in the United States and successfully launching commercial sales following any marketing approval;
- obtaining commercial acceptance of our products, if approved, by patients, the medical community and third-party payors and obtaining and maintaining healthcare coverage and adequate reimbursement;
- maintaining an acceptable safety profile following any marketing approval; and
- our ability to compete with other therapies.

Many of these factors are beyond our control, including the clinical development and regulatory approval process; potential threats to our intellectual property rights; and the manufacturing, marketing and sales efforts, respectively, of any current or future third-party contractors. If we are unable to develop, receive marketing approval for and successfully commercialize nalbuphine ER, or if we experience delays as a result of any of these factors or otherwise, our business would be substantially harmed.

Our approach to the development and commercialization of nalbuphine ER to treat serious neurologically mediated conditions is unproven.

We are currently focused on the development and commercialization of nalbuphine ER to treat serious neurologically mediated conditions. Nalbuphine ER is an oral extended release formulation of nalbuphine, which is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the United States and Europe. Nalbuphine is currently not commercially available in an oral dosage form, such as nalbuphine ER. While we believe that nalbuphine's dual mechanism of action, which targets both the central and peripheral nervous systems, makes nalbuphine ER a promising potential therapy for the treatment of chronic pruritus and other serious neurologically mediated conditions, and that nalbuphine ER has the potential to be safe and well-tolerated, nalbuphine has not been approved in any indications other than pain. Additionally, nalbuphine ER has not been approved in any indication, including the treatment of pruritus associated with prurigo nodularis, the lead indication for which we are pursuing clinical development of nalbuphine ER. No therapies have been approved in the United States or Europe for the treatment of moderate to severe pruritus, and we can provide no assurance that either nalbuphine ER or any other future product candidate that we may seek to develop for this indication or for any other serious neurologically mediated condition will be effective or safe, obtain regulatory approval or be commercially successful.

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

We are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements. We must complete extensive clinical trials to demonstrate the safety and efficacy of nalbuphine ER and any future product candidate in humans and complete required regulatory submissions before we will be able to obtain these approvals. We may never receive such approvals.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. The clinical development of nalbuphine ER and any future product candidate is susceptible to the risk of failure at any stage of product development and we may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent clinical development, marketing approval or commercialization of nalbuphine ER or any future product candidate, including:

- clinical trials may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to restructure clinical trials, conduct additional clinical and nonclinical trials or abandon product development programs;
- the number of patients required for clinical trials may be larger than we anticipate, patient enrollment in these clinical trials may be slower than we anticipate, whether as a result of the COVID-19 pandemic or otherwise, or participants may discontinue their participation in these clinical trials at a higher rate than we anticipate, as we experienced in our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis;
- the target number of patients in our PRISM trial may need to be increased as a result of the sample size re-estimation analysis, which may delay the timing of our report of the top-line data from this trial;
- the cost of planned clinical trials may be greater than we anticipate, as we have experienced in our Phase 2b/3 PRISM trial as we added additional sites, enrollment took longer than expected and we used additional incentive strategies to address site activation and enrollment;
- our clinical trials sites may not have adequate staff and resources to support our trials on a timely basis;
- our third-party contractors, including any that may be manufacturing a product candidate or drug substance or conducting clinical trials on our behalf, may deviate from applicable trial protocols, fail to comply with regulatory requirements or fail to meet their contractual obligations to us in a timely manner or at all;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with applicable clinical trial protocols, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;

- we may have to delay, suspend or terminate clinical trials for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, insufficient efficacy at any planned statistical re-estimations, or other unexpected characteristics of a product candidate;
- 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 their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our clinical trial designs or our interpretation of data from preclinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;
- the supply or quality of drug substance for our product candidates or the manufactured product candidate or other materials necessary to conduct clinical trials of the product candidate may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply;
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approvals; and
- the FDA or comparable foreign regulatory authorities may refuse to accept for substantive review any NDA, MAA or other comparable foreign regulatory application that we submit for a product candidate or may conclude after review of our data that our application is insufficient to obtain marketing approval of a product candidate.

In addition to the above, the continued spread of COVID-19 globally could adversely affect our clinical trial operations worldwide, including our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 if an outbreak occurs in their geography, and result in further delays in our clinical trials due to prioritization of hospital and medical resources toward the outbreak, restrictions in travel, potential unwillingness of patients to enroll in trials at this time, or the inability of patients to comply with clinical trial protocols if quarantines or travel restrictions impede patient movement or interrupt healthcare services. Furthermore, the response to the COVID-19 pandemic may redirect resources of regulators in a way that would adversely impact our ability to progress regulatory approvals. In addition, we may face impediments to regulatory meetings and approvals relating to our clinical trials due to measures intended to limit in-person interactions.

Under the protocol for our ongoing Phase 2b/3 PRISM trial, once approximately 50% of the patients are evaluable for the primary efficacy endpoint, an unblinded statistician for the trial will review the appropriate data, perform a sample size re-estimation, or SSRE, analysis and advise us on whether we should increase the number of patients in the trial or if we should stop the trial due to insufficient power to detect efficacy. If we determine to increase the number of patients in the trial based on the re-estimation, the costs of the trial may increase, the results of the trial may be delayed, and we may need to raise additional funds or divert resources from and delay our other programs to complete the trial.

If we are required to conduct additional clinical trials or other testing of nalbuphine ER or any future product candidate beyond the trials and testing that we contemplate, we are unable to successfully and timely complete clinical trials or other testing of nalbuphine ER or any future product candidate, the results of these trials or tests are unfavorable, uncertain or are only modestly favorable or there are unacceptable safety concerns associated with the product candidate, we may:

- incur additional unplanned costs, which may exceed the resources that we have available or are able to obtain on reasonable terms;
- experience delays in obtaining marketing approval for the applicable product candidate for several years or more, which could shorten the periods during which we may have the exclusive right to commercialize the product candidate or allow competitors to bring products to market before us;
- fail to obtain marketing approval at all;
- obtain marketing approval for indications or patient populations that are not as broad as we originally intended or desired;

- obtain marketing approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

Our failure to successfully and timely complete clinical trials of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated condition or of any future product candidate and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any such product candidates would significantly harm our business and could result in the loss or impairment of our ability to generate revenues and effectuate our business strategy.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of nalbuphine ER or any future product candidates, which would likely prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of nalbuphine ER or any future product candidate we must demonstrate through lengthy, complex and expensive clinical trials that the product candidate is both safe and effective for use in the target indication. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. It is possible that even if nalbuphine ER or any future product candidate has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. For example, our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis failed to meet its primary endpoint, and the number of patients who discontinued treatment prior to the end of the trial had a substantial impact on the results. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of nalbuphine ER or any future product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of, or intolerability caused by, nalbuphine ER or any future product candidate, or mistakenly believe that nalbuphine ER or any future product candidate is toxic or not well tolerated when that is not the case after the clinical evaluation is completed. Many pharmaceutical and biotechnology companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face setbacks as we continue our clinical development of nalbuphine ER and develop any other product candidates. It is also possible that any of our development programs could be placed on full or partial clinical hold by regulatory authorities at any point, which would delay and possibly prevent further development of those programs.

In addition, even if the clinical trials we plan are successfully completed and nalbuphine ER or any future product candidate achieves its specified endpoints in such trials, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we are able to submit product candidates for marketing approval. For example, patients with prurigo nodularis may have pruritus that is caused by dermatological conditions other than prurigo nodularis, and at a meeting with the FDA following the completion of our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, the FDA raised the need to adequately isolate a patient population with pruritus associated with prurigo nodularis for our planned Phase 3 clinical trials. While the inclusion criteria in our PRISM trial require that enrolled patients not be suffering from any active, uncontrolled dermatoses other than prurigo nodularis, it is possible that the FDA could conclude that this is not sufficient to identify patients suffering from pruritus associated with prurigo nodularis, in which case the FDA could question the overall validity of the results of the trial. To the extent that the results of our clinical trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, approval of product candidates may be significantly delayed, or we may be required to expend significant additional resources, which may not be available to us, to conduct additional trials in support of potential approval of product candidates. For instance, if nalbuphine ER does not achieve the primary endpoint in our PRISM trial, or the FDA does not otherwise believe that the results of the trial are sufficiently supportive of an application for marketing approval, the FDA may require us to conduct another Phase 3 clinical trial in addition to the PRISM trial and the additional Phase 3 clinical trial we plan to conduct, which would cause us to incur substantial additional costs and significantly delay our development of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis.

Use of patient-reported outcome assessments, or PROs, in our clinical trials and high placebo response rates may delay or impair the development of nalbuphine ER or adversely impact our clinical trials.

Due to the difficulty of objectively measuring pruritus, the assessment of pruritus in clinical trials typically involves the use of PROs. Our clinical trials evaluating the efficacy of nalbuphine ER in pruritus indications have used PROs as primary endpoints. For example, the primary endpoint of our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis was the proportion of patients reporting at least a 30% reduction from baseline to week 10 in seven-day mean Worst Itching Numerical Rating Scale, or WI-NRS, scores, which is a patient-reported assessment on an 11-point scale from 0 to 10 of the severity of the worst itch experienced in the last 24 hours. The primary endpoint of our PRISM trial is the proportion of patients achieving at least a 4-point improvement from baseline with respect to their worst itch at week 14 as measured by WI-NRS. PROs have an

important role in the development and regulatory approval of treatments for pruritus. However, PROs involve patients' subjective assessments of efficacy, and this subjectivity can increase the uncertainty of clinical trial outcomes assessing pruritus. Such assessments can be influenced by a number of factors and can vary widely from day to day for any particular patient, and from patient to patient and site to site within a clinical trial, leading to high variability in PRO measurements.

In addition, PROs for the assessment of pruritus have historically been observed to have high placebo group response rates. We observed this in some of our clinical trials of nalbuphine ER. For example, in our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, we observed a mean reduction from baseline in WI-NRS score for the trial's modified intention-to-treat population of 1.75 points for placebo as compared to 2.14 points for nalbuphine ER dosed twice-daily at 81 mg and 2.51 points for nalbuphine ER dosed twice-daily at 162 mg. The variability of PRO measures may be greater than other measures used for clinical trial assessments, and that variability can complicate clinical trial design, adversely impact the ability of a trial to show a statistically significant improvement and generally adversely impact a clinical development program by introducing additional uncertainties.

The variability of PRO measures and related high placebo response rates have adversely impacted clinical results of other therapies being tested for pruritus and could adversely impact our clinical development of nalbuphine ER. The FDA could also require changes in the PROs we are currently using or indicate that the PROs we are using are insufficient for demonstrating efficacy in pruritus, potentially delaying clinical development of nalbuphine ER, increasing our costs and making additional clinical trials necessary.

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 nalbuphine ER or any future product candidate if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials as required by the FDA or comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of our clinical trials and is affected by many factors, including:

- the impact of the COVID-19 pandemic;
- the size and nature of the eligible patient population;
- the severity of the disease under investigation;
- the proximity of eligible patients to clinical sites;
- patient referral practices of physicians;
- the eligibility criteria for the clinical trial;
- the design of the clinical trial;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications under investigation.

In particular, the successful completion of our clinical development program for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis is dependent upon our ability to enroll a sufficient number of patients with this severe condition. We have experienced delays and difficulties in the enrollment of patients in our clinical trials, including our PRISM trial and our Phase 2 clinical trial for chronic cough in patients with IPF, which have delayed the completion of our trials. We have taken actions to increase enrollment, including increasing the number of clinical sites, providing sites with additional trial management staff and closing underperforming sites. However, these actions may not be successful. In addition, as a result of the COVID-19 pandemic, clinical sites for our PRISM trial temporarily halted new patient screening and most patient enrollment, which will delay our ability to report top-line data for that trial, and our clinical sites have suspended enrollment and the treatment of patients in our ongoing Phase 2 clinical trial for chronic cough in patients with IPF due to the vulnerability of IPF patients to COVID-19, and multiple sites in both trials have begun requiring remote monitoring of patient data. We cannot presently predict how long these disruptions to enrollment may continue or whether they will worsen.

Other companies are conducting clinical trials or have announced plans for future clinical trials that are seeking, or are likely to seek, to enroll patients with prurigo nodularis in the case of our PRISM trial and patients with IPF in the case of our Phase 2 clinical trial for chronic cough in patients with IPF, and patients are generally only able to enroll in a single trial at a time. In addition, although there are no drugs approved in the United States or Europe for the treatment of pruritus associated with prurigo nodularis, many patients use various treatments off-label, such as antihistamines or gabapentin, and these patients and their physicians may be reluctant to forgo, discontinue or otherwise alter their use of such off-label therapeutic approaches to participate in our clinical trials.

Our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for nalbuphine ER or any future product candidate, delay or halt the development of and approval processes for such product candidate and jeopardize our ability to commence sales of and generate revenues from such product candidate, any of which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Adverse events or undesirable side effects caused by, or other unexpected properties of, nalbuphine ER or any future product candidate may be identified during development and could delay or prevent the marketing approval or limit the use of nalbuphine ER or any future product candidate.

Adverse events or undesirable side effects caused by, or other unexpected properties of, nalbuphine ER or any future product candidate could cause us, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of such product candidate and could result in a more restrictive label, or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. We cannot be certain that serious adverse events, or SAEs, will not occur in future clinical trials, which could cause the FDA or comparable foreign regulatory authorities to interrupt, delay or halt clinical trials of such product candidate, approve a more restrictive label than we desire or delay or deny regulatory approval.

In addition, nalbuphine ER, as a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist, may be susceptible to side effects associated with drugs having either of those mechanisms of action. κ-opioid receptor agonists have been associated with poorly tolerated psychiatric side effects, such as feelings of emotional and mental discomfort, or dysphoria, and hallucinations, at high doses. While we believe that the dual κ-opioid receptor agonist and μ-opioid receptor antagonist mechanism of action of nalbuphine reduces the likelihood of such psychiatric side effects, we have observed mild psychiatric side effects, including a few reported cases of mild euphoria, somnolence and feeling relaxed or feeling "high," in clinical trials of nalbuphine ER to date. μ-opioid receptor antagonists have the potential to precipitate withdrawal effects in patients, including drug addicts, and are associated with respiratory depression and potential cardiac risk. The drug label for nalbuphine, the active ingredient in nalbuphine ER, carries an opioid class label warning for serious, life-threatening or fatal respiratory depression, and nalbuphine ER, if approved for marketing in any indication, will likely carry a similar opioid class label. To support our planned submission of an NDA to the FDA for nalbuphine ER, we will be required to conduct a clinical trial of nalbuphine ER to assess cardiac risk and, due to the association of opioids with endocrine dysfunction, a clinical trial to evaluate potential endocrine side effects. We cannot be certain that any of these side effects often associated with opioids, or other side effects, will not be observed, or observed at more severe levels, in the future, or that the FDA will not require additional trials or impose more severe labeling restrictions due to these side effects or other concerns. Such drug-related side effects could also affect patient recruitment or the ability of enrolled patients to complete a trial or result in potential product liability claims.

In our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, the most frequently reported adverse events associated with nalbuphine ER were nausea, dizziness and headache. In the open label extension of the trial, nausea, dizziness and fatigue were reported. Across both the Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and the open label extension, a total of four patients reported SAEs, but none of these events was attributed to nalbuphine ER.

In our Phase 2b/3 trial of nalbuphine ER in patients with uremic pruritus, the most frequently reported adverse events attributed to nalbuphine ER were nausea, vomiting, somnolence and dizziness. In patients with uremic pruritus, SAEs were frequent but were primarily related to associated underlying diseases or to procedural complications related to hemodialysis.

If nalbuphine ER or any future product candidate is associated with adverse events or undesirable side effects or demonstrates unexpected properties, we may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that have initially shown promise in clinical or earlier stage testing were later discovered to cause undesirable or unexpected side effects or raised other safety issues that delayed or prevented further development of the compound.

Many currently approved μ-opioid products are subject to restrictive marketing and distribution regulations which, if applied to nalbuphine ER, could potentially restrict its use and harm our ability to generate profits.

Many currently approved μ-opioid receptor agonists require a Risk Evaluation and Mitigation Strategy, or REMS, as part of their approval by the FDA. REMS programs may require medication guides for patients, special communication plans to healthcare professionals or elements to assure safe use, such as restricted distribution methods, patient registries and/or other risk minimization tools. While nalbuphine ER has a μ-antagonist mechanism of action and has been well-tolerated in clinical trials to date, we have observed a few cases of mild euphoria, somnolence and feeling relaxed or feeling "high," which are characteristics that have led to misuse, abuse and addiction of μ-opioids. We plan to conduct a HAL study to further characterize the abuse potential of oral nalbuphine. If the results of the HAL study suggest that nalbuphine ER may carry risks of misuse, abuse or addiction, or even if the trial indicates that nalbuphine ER does not carry such risks, the FDA may require us to implement a REMS program in connection with any commercialization of nalbuphine ER. We cannot predict whether a REMS program would be required as part of FDA approval of nalbuphine ER and, if required, what requirements it might entail. Any limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensation of nalbuphine ER, if approved. If a REMS program is required, depending on the extent of the REMS requirements, the program might significantly increase our costs to commercialize nalbuphine ER. Furthermore, risks of nalbuphine ER that are not adequately addressed through a proposed REMS program for nalbuphine ER may also prevent or delay any approval for commercialization.

In addition, while nalbuphine is currently not classified as a controlled substance under the federal Controlled Substances Act of 1970, or the CSA, or the regulations of the U.S. Drug Enforcement Agency, or the DEA, it is the only opioid analgesic that is approved for marketing in the United States that is not classified as a controlled substance. It is possible that, based on the results of our HAL study, adverse events in our clinical trials or for other reasons, the DEA could determine that nalbuphine ER should be classified as a controlled substance. 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 carrying the greater level of regulatory control and Schedule V substances considered to present the lowest relative risk of abuse among such substances and, accordingly, the lowest level of regulatory control. Various states also independently regulate controlled substances. Though state-controlled substance laws often mirror federal law, because the states are separate jurisdictions, they may separately regulate drugs as well. While some states automatically classify a drug when the DEA does so, in other states there must be rulemaking or a legislative action. Regulatory authorities in foreign jurisdictions may also determine to classify nalbuphine ER as a controlled substance under different, but potentially no less burdensome, regulations.

If nalbuphine ER is classified as a controlled substance, the level of regulation would depend on how it is scheduled, and we and our suppliers, manufacturers, contractors, distributors and any future customers would be required to obtain and maintain any applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with any applicable state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. Also, if nalbuphine ER is classified as a controlled substance, there is a risk that such regulations could limit its supply for use in clinical trials and, in the future, limit our ability to produce and distribute nalbuphine ER in the volume needed to meet potential commercial demand.

Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, record keeping, 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. If nalbuphine ER is classified as a controlled substance, failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing nalbuphine ER 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 the restrictive nature of these regulations, if nalbuphine ER is classified as a controlled substance, depending on how it is scheduled, its commercial prospects could be limited.

Results of preclinical studies and clinical trials may not be predictive of results of later clinical trials.

The outcome of preclinical studies and clinical trials may not be predictive of the success of later clinical trials, and preliminary or interim results of clinical trials do not necessarily predict final results. For instance, nalbuphine ER or any future product candidate may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in preclinical studies or successfully advancing through Phase 1 and Phase 2 clinical trials. Many pharmaceutical and biotechnology companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier stages of clinical development, and we could face similar setbacks. Similarly, the design of a clinical trial can determine whether its results will support marketing approval of a product and adjustments in the design of a clinical trial may not be possible once the clinical trial has commenced.

At a meeting with the FDA following the completion of our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, the FDA advised us that the findings of the Phase 2 clinical trial may not be reliable and recommended that we conduct an additional Phase 2 dose ranging trial to identify the optimal dose and obtain reliable estimates of treatment effect for the recommended primary efficacy endpoint so as to better design and power our planned Phase 3 clinical trials. In providing such advice, the FDA noted the small number of patients in each arm of the Phase 2 clinical trial and the large differential discontinuation rate among the three treatment arms, as well as our plan to increase the fixed-dose treatment duration from eight weeks in the Phase 2 clinical trial to 12 weeks in our PRISM trial.

We have limited experience in designing pivotal clinical trials, and flaws in the design of a clinical trial could result in significant delays in completing the clinical trial or may require us to abandon the clinical trial altogether or conduct additional clinical trials. For example, we have designed our PRISM trial based on an assumed discontinuation rate that takes into account observed discontinuation rates in our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis. If enrolled patients withdraw from our PRISM trial at a rate that is higher than expected, as occurred in our Phase 2 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis, or at rates that are inconsistent across clinical sites and treatment arms, we may not achieve the primary endpoint of the trial, the validity or statistical significance of the trial could be impaired and regulatory authorities may not view the trial as supportive of an application for marketing approval. Preclinical and clinical data are also often susceptible to varying interpretations and analyses. Many pharmaceutical and biotechnology companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for those product candidates. Even if we believe that the results of clinical trials for nalbuphine ER or any future product candidate warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of the product candidate.

In addition, some of our data for nalbuphine ER for the treatment of pruritus is drawn from *post hoc* analyses of data subsets from our Phase 2 clinical trials of nalbuphine ER in patients with prurigo nodularis and uremic pruritus. While we believe these data may be useful in informing the design of our PRISM trial and other future Phase 3 clinical trials for nalbuphine ER, *post hoc* analyses performed after unmasking trial results can result in the introduction of bias and may not be predictive of success in Phase 3 clinical trials.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of patient populations, changes in and adherence to dosing regimens and other clinical trial protocols, as well as the rate of discontinuation among clinical trial participants. If we fail to receive positive results in clinical trials of nalbuphine ER or any future product candidate, the development timeline and regulatory approval and commercialization prospects for those product candidates and, correspondingly, our business and financial prospects would be negatively impacted.

Even if nalbuphine ER or any future product candidate receives marketing approval, we or others may later discover that the product is less effective than previously believed or that it causes undesirable side effects that were not previously identified, which could compromise our ability to market the product.

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

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

Any of these events could harm our business and operations and could negatively impact our stock price.

Even if nalbuphine ER or any future product candidate 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, in which case the market opportunity for nalbuphine ER may be smaller than we estimate and we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if nalbuphine ER or any future product candidate is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market and may be reluctant to prescribe opioid-based therapies due to perceived risks of misuse, abuse and addiction. Further, patients often acclimate to their current therapies and do not want to switch unless their physicians recommend changing products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of nalbuphine ER or any future product candidate may require significant resources and may not be successful. If nalbuphine ER or any future product candidate is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of nalbuphine ER or any future product candidate, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential and perceived advantages of the product compared to other therapies;
- the prevalence and severity of any side effects;
- the potential that the DEA could determine that nalbuphine ER should be classified as a controlled substance;
- the clinical indications for which the product is approved;
- whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy;
- our ability to offer the product for sale at competitive prices;
- the product's convenience and ease of administration;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- limitations or warnings, including distribution or use restrictions contained in the product's approved labeling;
- the strength of sales, marketing and distribution support for the product;
- the approval of other new products for the same indications;
- the timing of market introduction of the product as well as competitive products;
- adverse publicity about the product or favorable publicity about competitive products;
- potential product liability claims;
- changes in the standard of care for the targeted indications for the product; and
- availability and amount of coverage and reimbursement from government payors, managed care plans and other third-party payors.

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

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. For example, we currently intend to focus our resources on the development of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis as our lead program. However, the development of nalbuphine ER for this indication may ultimately prove to be unsuccessful or less successful than another product candidate or other indications that we might have chosen to pursue with our limited resources.

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 development programs and product candidates for specific indications may not yield any commercially viable product candidates. 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 the product candidate.

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

We do not currently have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. If nalbuphine ER receives marketing approval from the FDA in any of our target indications, we believe we will have the opportunity to commercialize it in the United States directly through our own focused, specialty sales organization. If nalbuphine ER receives marketing approval outside the United States, we may develop a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize the product in those markets.

We plan to build focused capabilities to commercialize development programs for certain indications where we believe that medical specialists are sufficiently concentrated to allow us to effectively promote products with a specialty sales team. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. We could prematurely or unnecessarily incur commercialization costs if the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason. This may be costly, and our business and financial prospects could be significantly affected if we could not retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain an adequate sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

In certain indications and markets, we may seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize nalbuphine ER or any future product candidate. We may also seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be substantially lower than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

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

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

The development and commercialization of new products is highly competitive. We expect that we will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to nalbuphine ER or any future product candidate that we may seek to develop or commercialize. Our competitors may succeed in developing, acquiring or licensing technologies and products that are more effective, have fewer or more tolerable side effects or are more convenient or less costly than nalbuphine ER or any future product candidate we may develop, which could render any product candidates obsolete and noncompetitive. Our competitors also may obtain FDA or other marketing approval for their products before we are able to obtain approval for ours, which could result in competitors establishing a strong market position before we are able to enter the applicable market.

If nalbuphine ER is approved for the treatment of pruritus associated with prurigo nodularis, we expect that it would compete with a number of therapeutics that are used off-label to treat prurigo nodularis, including anti-itch creams and emollients, oral or injectable antihistamines, Dupixent (dupilumab), which is an injectable prescription medicine approved for atopic dermatitis that is in clinical development for the treatment of pruritus associated with prurigo nodularis, gabapentin and Lyrica (pregabalin), which are prescription medicines approved for the treatment of seizures and neuropathic pain, naltrexone and UVB light therapy. We also expect that nalbuphine ER might compete with product candidates currently in clinical development in this indication, including nemolizumab, an anti-interleukin-31 receptor A humanized monoclonal antibody being developed by Galderma; and KPL-716, a monoclonal antibody targeting oncostatin M receptor beta being developed by Kiniksa Pharmaceuticals. In addition, a number of other product candidates are currently in clinical development to treat other pruritic conditions and nalbuphine ER, if approved for the treatment of pruritus associated with prurigo nodularis could face competition from these product candidates, including tradipitant, an oral neurokinin-1 receptor antagonist being developed by Vanda Pharmaceuticals that is in Phase 3 clinical trials for chronic pruritus in patients with atopic dermatitis.

If nalbuphine ER is approved for the treatment of pruritus associated with primary biliary cholangitis, or PBC, we expect that it would compete with a number of therapeutics that are used off-label to treat pruritus associated with chronic liver disease, including PBC, which may include bile acid sequestrants, such as cholestyramine, which are used off-label and generally as first-line therapy, although they typically provide only modest relief. Cholestyramine is marketed as Questran in the United States and as Colestyr, Efensol, Ipocol, Kolestran, Lipocol, Olestyr, Prevalite or Quantalan in various other countries. Treatment of pruritus associated with chronic liver disease, including PBC, may also include second-line therapies such as the antibiotic rifampicin, naltrexone, the anti-depressant sertraline, as well as phototherapy and drugs such as gabapentin and Lyrica (pregabalin), which are prescription medicines approved for the treatment of seizures and neuropathic pain. We also expect that nalbuphine ER might compete with product candidates currently in clinical development in this indication, including Korsuva (difelikefalin), an orally administered κ-opioid receptor agonist being developed by Cara Therapeutics, and linerixibat, an ileal bile acid transporter inhibitor being developed by GlaxoSmithKline, both of which are in Phase 2 clinical trials for pruritus associated with PBC. In addition, it is possible that therapies to reduce chronic liver disease, such as ursodeoxycholic acid, which is approved for the treatment of PBC, could reduce the need for therapies to treat pruritus associated with chronic liver disease, including PBC.

If nalbuphine ER is approved for the treatment of chronic cough associated with idiopathic pulmonary fibrosis, or IPF, we expect that it would compete with product candidates currently in development for the treatment of chronic cough associated with IPF, such as RVT-1601, a formulation of cromolyn sodium being developed by Respivant Sciences, and expect that it might also compete with other product candidates currently in development for the treatment of chronic cough by companies including Merck, Shionogi, Bellus Therapeutics and Nerre Therapeutics. In addition, it is possible that product candidates currently in development for the treatment of IPF could, if approved, reduce the need for therapies to treat chronic cough associated with IPF.

If nalbuphine ER is approved for the treatment of levodopa-induced dyskinesia, or LID, in patients with Parkinson's disease, we expect that it would compete with Gocovri and Osmolex, which are extended release capsule formulations of amantadine marketed by Adamas Pharmaceuticals and Osmotica, respectively, and expect that it might also compete with other product candidates currently in development for the treatment of LID by companies including Addex Therapeutics and IRLAB Therapeutics. In addition, it is possible that product candidates currently in development for the treatment of Parkinson's disease by companies could, if approved, reduce the need for therapies to treat LID.

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

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

Once an NDA is approved, the product covered thereby becomes a "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. It is unclear whether the FDA will treat the active ingredients in our product candidates as NCEs and, therefore, afford them five years of NCE data exclusivity if they are approved. If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition from generic versions of any products we develop could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those products.

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

The commercial success of any product we develop will depend substantially, both in the United States and other countries, on the extent to which the costs of the product will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement are not available, or reimbursement is available only to limited levels, we may not be able to successfully commercialize that product. Even if coverage is provided for the product, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a return on our investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of any product we commercialize to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

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

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability to commercialize any product candidate will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and other countries. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell products profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us to decrease the price we might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

The commercial potential of any products we are able to commercialize depends in part on reimbursement by government health administration authorities, private health insurers and other organizations. If we are unable to obtain coverage or reimbursement for those products at the levels anticipated, our financial condition could be harmed. Additionally, if new compounds currently in development by potential competitors obtain marketing approval, there may be downward pressure on reimbursement levels for therapies in our target indications, which could have a negative impact on our ability to achieve and maintain profitability.

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

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

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

We face an inherent risk of product liability claims as a result of our clinical trials, despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we commercialize any product 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. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

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

Although we maintain product and clinical trial liability insurance of at least $5.0 million in the aggregate, our insurance coverage may not fully cover potential liabilities that we may incur. The cost of any product or clinical trial liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if we commercialize any product that receives marketing approval. If we are unable to maintain sufficient insurance coverage at an acceptable cost or otherwise protect against potential clinical trial liability or product liability claims, the development and commercial production and sale of nalbuphine ER or any future product candidate could be prevented or inhibited, which could harm our business, financial condition, results of operations and prospects.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our clinical trials. If they do not perform satisfactorily, our business could be harmed.

We do not independently conduct clinical trials of our product candidate. We rely, and expect to continue to rely, on third parties, such as clinical research organizations, or CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials of nalbuphine ER and any future product candidate that we may develop. These third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. In addition, there is a natural transition period when a new CRO begins work on a clinical trial. As a result, delays would likely occur, which could negatively impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects.

Further, although our reliance on these third parties for clinical development activities limits our control over these activities, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, as well as applicable legal, regulatory and scientific standards. Moreover, the FDA requires us to comply with standards, commonly referred to as current Good Clinical Practices, or cGCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these cGCPs through periodic inspections of clinical trial sponsors, principal investigators, clinical trial sites and institutional review boards. If we or our third-party contractors fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving the applicable product candidate, which would delay the marketing approval process. We cannot be certain that, upon inspection, the FDA will determine that any of our clinical trials complies with cGCPs. Similar regulatory requirements apply outside the United States, including the International Council for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, or ICH. We are also required to register clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, the third parties conducting clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with our contractors, we cannot control whether they devote sufficient time, skill and resources to our ongoing development programs. These third parties may be also impacted by developments in the COVID-19 pandemic or government measures taken in response to the pandemic in ways that negatively impact their ability to fulfill their contractual obligations to us in connection with our clinical trials, even if we are not otherwise directly affected by such developments or measures. Additionally, these third parties may have relationships with other commercial entities, including potential competitors, for which they may also be conducting clinical trials or other drug development activities, which could impede their ability to devote appropriate time to our clinical programs. Third parties may not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our protocols. For example, we have terminated clinical investigators from our previous clinical trials due to suspected non-compliance with regulatory requirements. If the third parties on which we rely do not carry out their duties, meet their deadlines or comply with regulatory requirements, we will not be able to, or may be delayed in our efforts to, successfully commercialize nalbuphine ER or any future product candidate. In such an event, our financial results and the commercial prospects for any product candidates that we seek to develop could be harmed, our costs could increase and we may not be able to generate revenues or become profitable.

We contract with third parties for the manufacture, storage, packaging and distribution of nalbuphine ER for clinical trials, including a single supplier for the active ingredient, and expect to continue to rely on third parties for these services in connection with our future development and commercialization efforts for nalbuphine ER and any future product candidates.

We currently have no manufacturing facilities and a relatively small number of personnel with sufficient experience to oversee the manufacturing process. We rely, and plan to continue to rely, on contract manufacturers and other third-party contractors to manufacture, store, package and distribute both drug substance and drug product for our clinical trials. If any of our product candidates receive regulatory approval, we plan to continue to rely upon contract manufacturers, and, potentially, collaboration partners, to manufacture commercial quantities of such products. We may be unable to establish any further agreements with contract manufacturers or any other third-party contractors, or may fail to do so on acceptable terms or when needed. Even if we are able to establish agreements with such third-party contractors, reliance on third-party contractors entails additional risks, including:

- manufacturing delays if our third-party contractors prioritize the supply of other companies' products over nalbuphine ER or any future product candidates or otherwise fail to satisfactorily perform according to the terms of the agreements between us and them, or if unforeseen events in the manufacturing process arise;
- the possible termination or nonrenewal of agreements by our third-party contractors at a time that is costly or inconvenient for us;
- the possible breach by third-party contractors of our agreements with them;
- the failure of third-party contractors to comply with applicable regulatory requirements;
- the possible mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified;
- the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

We do not have long-term supply agreements with any of our contract manufacturers. If any of our existing manufacturers should become unavailable to us for any reason, including as a result of the COVID-19 pandemic or government measures taken in response to the pandemic, we may incur delays in identifying or qualifying replacements. Any performance failure on the part of our contract manufacturers or the other third-party contractors that we use to store and distribute drug substance and drug product could be disruptive to our operations and delay clinical development or marketing approval of nalbuphine ER or any future product candidates of ours or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue.

We also rely, and plan to continue to rely, on a single supplier, Mallinckrodt, for nalbuphine hydrochloride drug substance. We do not have agreements in place with Mallinckrodt that guarantee supply quantities or pricing. Any significant delay in acquisition, increase in cost or decrease in availability of nalbuphine hydrochloride drug substance could considerably delay the manufacture of nalbuphine ER, which could adversely impact the timing of our current and planned clinical trials and potential regulatory approval and commercialization of nalbuphine ER. Although we believe there are alternate sources of supply that could satisfy our clinical and commercial requirements for nalbuphine drug substance, we have not qualified any alternate sources and cannot assure you that we would be able to establish relationships with any such sources in a timely fashion, on commercially reasonable terms or at all.

If nalbuphine ER or any future product candidates are approved by any regulatory agency, we will need to enter into agreements with third-party contract manufacturers for the commercial production and distribution of those products. In addition, we may face competition for access to manufacturing facilities as there may be a limited number of contract manufacturers operating under cGMPs that are able manufacture any such product. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, in a timely manner or at all, which could delay our commercialization efforts.

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

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

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

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

While we have not entered into any collaborations to date, we may seek to establish one or more collaborations for the development and commercialization of nalbuphine ER or any future product candidate. Potential collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies, biotechnology companies and academic research institutions. In addition, if we are able to obtain marketing approval for any product candidates from foreign regulatory authorities, we intend to enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of those product candidates outside of the United States.

We face significant competition in seeking appropriate collaborators. There have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidates from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and existing or potential competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than a collaboration with us. Any collaboration agreements that we enter into in the future may also contain restrictions on our ability to enter into other potential collaborations or to develop specified product candidates. We may not be able to negotiate collaborations on a timely basis, on acceptable terms or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay the potential commercialization of such product candidate, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

If we establish one or more collaborations, all of the risks relating to product development, regulatory approval and commercialization described in this Quarterly Report on Form 10-Q would also apply to the activities of any such future collaborators.

If we enter into collaborations with third parties for the development or commercialization of nalbuphine ER or any future product candidate, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We may seek to enter into collaborations with third parties for the development or commercialization of nalbuphine ER or any future product candidate. If we enter into any such collaborations, we would have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of any such product candidates. Our ability to generate revenues from these arrangements would depend on any future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving a product candidate would 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 not pursue development and commercialization of the product candidates under the collaboration or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition of the collaborator, that divert resources or create competing priorities;
- collaborators may be involved in a business combination, and could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed by us;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with the product candidates under the collaboration;
- collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability, or misappropriate our intellectual property or other proprietary information;
- collaborators may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements;
- disputes may arise between the collaborators and us regarding ownership of or other rights in the intellectual property generated in the course of the collaborations; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all.

Risks Related to Our Intellectual Property

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are critical to our business or owe damages to the licensor of such intellectual property.

We are party to an exclusive license agreement with Endo Pharmaceuticals Inc. under which we have licensed certain patent rights and know-how to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including an extended release formulation such as nalbuphine ER. We are also party to an exclusive license agreement with Rutgers University under which we have licensed certain patent rights and know-how to develop and commercialize products incorporating nalbuphine for any human or animal use. We may in the future seek additional licenses from others to develop and commercialize additional product candidates or technologies. These licenses may not provide exclusive rights to use the relevant intellectual property in all desired fields of use and in all territories in which we may wish to develop or commercialize product candidates in the future. It is also possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all.

Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, development and commercialization, milestone payment, royalty and other obligations on us. If we fail to comply with our material obligations under these agreements, or if we are subject to a bankruptcy event, the licensor may have the right to terminate the license or convert the license to a non-exclusive license, in which event we may be required to negotiate a new or reinstated license with less favorable terms or would not be able to exclusively market, or market at all, products covered by the license. Any such event could have a material adverse impact on our business.

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

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

If disputes over intellectual property that we license prevent or impair our ability to maintain those license arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize any affected product candidates.

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to nalbuphine ER and any future product candidates. If we do not adequately protect our intellectual property rights, competitors may erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we have licensed exclusive rights under patents, prosecuted additional patents and filed patent applications in the United States and other countries related to methods of use and formulations of nalbuphine ER. The patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost, in a timely manner or at all.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain or successfully enforce necessary or desirable patent protection from those patent rights. We may not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we may license, and therefore cannot guarantee that these patents and applications will be prosecuted in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors or other responsible third parties have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If we, our licensors or any future partners, collaborators, licensors or licensees fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our licensors or any future partners, collaborators, licensors or licensees disagree or do not fully cooperate with us as to the prosecution, maintenance or enforcement of any patent rights, those patent rights could be compromised. We, our licensors and any future partners, collaborators, licensors and licensees may also fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to strengthen our patent position. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

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

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed patent applications on inventions claimed in our patents or applications on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and other countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or to other patent offices around the world. Alternatively or additionally, we may become involved in post-grant review procedures, oppositions, derivation, proceedings, reexaminations, inter partes review or interference proceedings, in the United States or other countries, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenge may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical products or product candidates, or limit the duration of the patent protection of nalbuphine ER or any future product candidates of ours. In addition, given the amount of time required for the development, testing and regulatory review of new

product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Furthermore, while it is our policy to require our employees and contractors who may be involved in the conception or 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, conceives or develops intellectual property that we regard as our own. As a result, the inventorship or ownership of our intellectual property may be challenged in the future.

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, patent laws in various jurisdictions, including significant commercial markets such as Europe, restrict the patentability of methods of treatment of the human body more than United States law does.

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

Pursuant to the terms of our license agreements with third parties, we have the right, but not the obligation, to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents. Even if we pursue such enforcement or defense, we will require the cooperation of our licensors, and cannot guarantee that we would receive it and on what terms. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. If we cannot obtain patent protection, or enforce existing or future patents against third parties, our competitive position and our financial condition could suffer.

If we are unable to protect the confidentiality of our trade secrets, the value of our products could be negatively impacted and our business would be harmed.

In addition to the protection afforded by patents, we also rely on trade secret protection for certain aspects of our intellectual property. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, independent contractors, advisors, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. Further, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

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

Our competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that one of our patents is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years and require substantial resources. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming, its outcome would be uncertain and it could prevent or delay us from developing or commercializing nalbuphine ER or any future product candidate.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell products without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds and methods of use for the treatment of the disease indications for which we are developing, or may in the future develop, nalbuphine ER or any future product candidate. If any third-party patents or patent applications are found to cover nalbuphine ER or any future product candidate or their methods of use, we may not be free to manufacture or market the product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our nalbuphine ER or any future product candidates, including interference proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to nalbuphine ER or any future product candidate. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that nalbuphine ER or any future product candidate may be accused of infringing. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the relevant patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. 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; alternatively or additionally, it could include terms that impede or eliminate our ability to compete successfully in the commercial marketplace. 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 nalbuphine ER or any future product candidate or force us to cease some of our business operations, which could 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.

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

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reformed United States patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system, expanding the definition of prior art, and developing a post-grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post-grant review and inter partes review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for inter partes review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for inter partes review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas inter partes review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U.S. patent invalidated in a USPTO post-grant review or inter partes review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to enforce our patents. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States are less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products. Our competitors may export otherwise infringing products to territories where we have no patent protection or where we may obtain patent protection, but where patent enforcement is not as strong as that in the United States, and our issued or licensed patents and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property rights in major markets for any products that we are able to develop, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market any such products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

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 and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, including some which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure, non-competition and non-solicitation agreements, or similar agreements, in connection with such previous employment. 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 we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize nalbuphine ER or any future product candidate. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such 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. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, the failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering nalbuphine ER or any future product candidate, our competitive position would be adversely affected.

If we are unable to obtain licenses from third parties on commercially reasonable terms, our business could be harmed.

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize nalbuphine ER or any future product candidate, in which case we would be required to obtain a license from these third parties. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business, and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales or an obligation on our part to pay royalties and/or other forms of compensation in connection with any sales we make. Even if we are able to obtain a license, it may be non-exclusive, which could enable our competitors to obtain access to the same technologies licensed to us.

Risks Related to Regulatory Approval and Other Legal Compliance Matters

If the FDA does not conclude that nalbuphine ER for the treatment of pruritus associated with prurigo nodularis or any other development program satisfies the requirements under Section 505(b)(2) of the FDCA, or Section 505(b)(2), or if the requirements for such programs are not as we expect, the approval pathway for these programs will likely take significantly longer, cost significantly more and entail significantly greater complications and risks than anticipated, and in any case may not be successful.

We commenced our Phase 2b/3 PRISM trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and expect to conduct an additional Phase 3 clinical trial of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis under the FDA's Section 505(b)(2) regulatory pathway. The Drug Price Competition and Patent Term Restoration Act of

1984, or the Hatch-Waxman Act, added Section 505(b)(2) to the FDCA. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies that were not conducted by or for the applicant, and for which the applicant has not received a right of reference, which could expedite the development program for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and any future product candidates by potentially decreasing the amount of preclinical and clinical data that we would need to generate in order to obtain FDA approval. However, while we believe that nalbuphine ER is a reformulation of an existing drug or biologic and, therefore, will not be treated as a new chemical entity, or NCE, the submission of an NDA under the Section 505(b)(2) or similar regulatory pathway does not preclude the FDA from determining that nalbuphine ER is an NCE and therefore not eligible for review under such regulatory pathway.

If the FDA does not allow us to pursue the Section 505(b)(2) or similar regulatory pathway as anticipated, we may need to conduct additional preclinical experiments and clinical trials, provide additional data and information and meet additional standards for regulatory approval. If this were to occur, the time and financial resources required to obtain FDA approval for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis and any future product candidates, and complications and risks associated with these product candidates, would likely increase significantly. Moreover, inability to pursue the Section 505(b)(2) or similar regulatory pathway could result in new competitive products reaching the market more quickly than our product candidates, which would likely harm our competitive position and prospects. Even if we are allowed to pursue the Section 505(b)(2) or similar regulatory pathway, our product candidates may not receive the requisite approvals for commercialization.

In addition, notwithstanding the approval of a number of products by the FDA under Section 505(b)(2) over the last few years, certain competitors and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, the FDA may be required to change its 505(b)(2) policies and practices, which could delay or even prevent the FDA from approving any NDA that we submit under Section 505(b)(2). In addition, the pharmaceutical industry is highly competitive, and Section 505(b)(2) NDAs are subject to special requirements designed to protect the patent rights of sponsors of previously approved drugs that are referenced in a Section 505(b)(2) NDA. These requirements may give rise to patent litigation and mandatory delays in approval of our potential future NDAs for up to 30 months depending on the outcome of any litigation. It is not uncommon for a manufacturer of an approved product to file a citizen petition with the FDA seeking to delay approval of, or impose additional approval requirements for, pending competing products. If successful, such petitions can significantly delay, or even prevent, the approval of the new product. However, even if the FDA ultimately denies such a petition, the FDA may substantially delay approval while it considers and responds to the petition. In addition, even if we are able to utilize the Section 505(b)(2) regulatory pathway for our product candidates, there is no guarantee this would ultimately lead to faster product development or earlier approval.

Moreover, even if our product candidates are approved under the Section 505(b)(2) pathway, the approval may be subject to limitations on the indicated uses for which the products may be marketed or to other conditions of approval, or may contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the products.

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of nalbuphine ER or any future product candidate. As a result, we cannot predict when or if, and in which territories, we will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We are not permitted to market nalbuphine ER or any other product candidate in the United States until we receive approval of an NDA from the FDA or in other countries until we receive marketing approval from the applicable regulatory authorities outside the United States. We have not submitted an application for or received marketing approval for any product candidate in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA.

The process of obtaining marketing approvals, both in the United States and other countries, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authorities. The FDA or other regulatory authorities may determine that nalbuphine ER or any future product candidate is not safe and effective, only moderately effective or has undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. 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.

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

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

We have conducted, are conducting and intend in the future to conduct clinical trials for nalbuphine ER, and may conduct clinical trials for any future product candidates, at sites outside the United States. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the United States could subject us to additional delays and expense.

We have conducted, are conducting and intend in the future to conduct clinical trials for nalbuphine ER, and may conduct clinical trials for any future product candidates, at trial sites that are located outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with cGCPs. The FDA must be able to validate the data from the trial, including, if necessary, through an onsite inspection. The trial population must also have a similar profile to the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful, except to the extent the disease being studied does not typically occur in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of nalbuphine ER or the applicable future product candidate.

In addition, the conduct of clinical trials outside the United States could have a significant adverse impact on us. Risks inherent in conducting international clinical trials include:

- clinical practice patterns and standards of care that vary widely among countries;
- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange rate fluctuations; and
- diminished protection of intellectual property in some countries.

Failure to obtain marketing approval in foreign jurisdictions would prevent nalbuphine ER or any future product candidate from being marketed in other countries. Any marketing approval we are granted in the United States would not assure marketing approval in foreign jurisdictions.

In order to market and sell products in the European Union and other foreign jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We 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. We may file for marketing approvals but not receive necessary approvals to commercialize any products in any market. Obtaining non-U.S. regulatory approvals and compliance with non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of any product candidates in any country. In addition, if we fail to obtain the non-U.S. approvals required to market products outside the United States or if we fail to comply with applicable non-U.S. regulatory requirements, our target markets will be reduced and our ability to realize the full market potential of nalbuphine ER or any future product candidate will be harmed and our business, financial condition, results of operations and prospects may be adversely affected.

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

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

A fast track designation, grant of priority review status or breakthrough therapy status by the FDA is not assured and, in any event, may not actually lead to a faster development or regulatory review or approval process and, moreover, would not assure FDA approval of nalbuphine ER or any future product candidate.

We may be eligible for fast track designation, priority review or breakthrough therapy status for product candidates we may develop. If a product candidate is intended for the treatment of a serious or life-threatening disease or condition and the product candidate demonstrates the potential to address unmet medical needs for this disease or condition, the product candidate sponsor may apply for FDA fast track designation. If a product candidate offers major advances in treatment, the product candidate sponsor may apply for FDA priority review status. Additionally, a product candidate may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA has broad discretion whether or not to grant these designations, so even if we believe a particular product candidate is eligible for such designation or status, the FDA could decide not to grant it. Moreover, even if we do receive such a designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures and there is no assurance that the product candidate will be approved by the FDA.

Even if we obtain marketing approvals for a product, the terms of approvals and ongoing regulation of such product may limit how we manufacture and market the product, which could impair our ability to generate revenue.

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

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

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

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

We expect that any regulatory approval to market nalbuphine ER in the United States will be limited by indication. If we fail to comply or are found to be in violation of FDA and other regulations restricting the promotion of nalbuphine ER for unapproved uses, we could be subject to criminal penalties, substantial fines or other sanctions and damage awards.

If our clinical trials are successful, we intend to seek approval to market nalbuphine ER for the treatment of pruritus associated with prurigo nodularis. If we obtain regulatory approval to market nalbuphine ER with an indication statement for the treatment of pruritus associated with prurigo nodularis, we expect to be prohibited from marketing nalbuphine ER using any promotional claims relating to treatment of pruritus generally. Marketing of nalbuphine ER may also be limited by regulatory authorities based on use as a monotherapy or adjuvant, concomitant medications, severity of pruritus and other factors.

The regulations relating to the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA, EMA and other government agencies. While we have, and may in the future conduct, clinical trials to evaluate the use of nalbuphine ER to treat pruritic conditions other than pruritus associated with prurigo nodularis, nalbuphine ER cannot be promoted for uses other than uses approved in the labeling by the FDA, EMA or other applicable regulatory authorities. Physicians may nevertheless prescribe nalbuphine ER off-label to their patients in a manner that is inconsistent with the approved label. We intend to implement compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations. Notwithstanding these programs, the FDA or other government agencies may allege or find that our practices constitute prohibited promotion of nalbuphine ER for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses.

In recent years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys' Offices, the Office of Inspector General of the Department of Health and Human Services, the FDA, the Federal Trade Commission and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the FDCA, the False Claims Act, the Prescription Drug Marketing Act and anti-kickback laws, and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. Many of these investigations originate as "*qui tam*" actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim, or caused a false claim to be submitted, to the government for payment. The person bringing a *qui tam* suit is entitled to a share of any recovery or settlement. *Qui tam* suits, also commonly referred to as "whistleblower suits," are often brought by current or former employees. In a *qui tam* suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone.

If the FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a *qui tam* suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation.

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

Any product for which we obtain marketing approval, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such product, among other things, will be subject to 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, 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 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.

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

In addition, later discovery of previously unknown adverse events or other problems with any product for which we may obtain marketing approval and its manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such product, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of the product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the product from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of the product;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of the product;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Under the 21st Century Cures Act and regulatory reform initiatives of the current presidential administration, the FDA's policies, regulations and guidance may be revised or revoked, which could prevent, limit or delay regulatory approval of nalbuphine ER or any future product candidate, impacting our ability to generate revenue.

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or other countries. For example, certain policies of the current presidential administration may impact our business and industry. Namely, the current presidential administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-resourced FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. In January 2017, the President issued an executive order applicable to all executive agencies, including the FDA, which required that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall have identified at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that required the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or

repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and Budget in February 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, the President issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations. It is difficult to predict how these various requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Current and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize nalbuphine ER or any future product candidate and may affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of nalbuphine ER or any future product candidate, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we may receive for any approved products.

In March 2010, then-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 ACA. Among the provisions of the ACA of potential importance to our business and nalbuphine ER or any future product candidate are the following:

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

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2027 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any product for which we may obtain regulatory approval or the frequency with which any such product is prescribed or used.

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

Since enactment of the ACA, there have been , and continue to be numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress may consider other legislation to replace elements of the ACA during the next Congressional session.

The current presidential administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, the President has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. This decision is under review by the U.S. Supreme Court during its current term. The full effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. In addition, Centers for Medicare & Medicaid Services, or CMS, has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

In addition, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The current presidential administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The current presidential administration recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On March 3, 2020, the U.S. Supreme Court agreed to review this decision. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We plan to continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop commercialize product candidates.

Further, there have been several recent U.S. congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, the current presidential administration has pressed for further drug price control measures to be enacted in 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. Any proposed measures will require authorization through additional legislation to become effective, and Congress and the current presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. It is unclear, however, whether the Congress and administration will be able to reach agreement on any such measures in the foreseeable future.

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

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

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

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

Any relationships we may have with customers, healthcare providers and professionals, and third-party payors, among others, will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we are able to obtain marketing approval. Any arrangements we have with healthcare providers, third-party payors and customers will subject us to broadly applicable fraud and abuse and other healthcare laws and regulations. The laws and regulations may constrain the business or financial arrangements and relationships through which we conduct clinical research, market, sell and distribute any products for which we obtain marketing approval. These include the following:

Anti-Kickback Statute. The federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), 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, lease or order of a good, facility, item or service for which payment may be made under a federal healthcare program such as Medicare and Medicaid.

False Claims Laws. The federal false claims and civil monetary penalties laws, including the federal civil False Claims Act, impose criminal and civil penalties, including through civil whistleblower or *qui tam* actions against individuals or entities for, among other things, knowingly presenting or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties.

HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for, among other things, executing a scheme, or making materially false statements in connection with the delivery of or payment for health care benefits, items or services. Additionally, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations on covered entities and their business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information.

Transparency Requirements. The federal Physician Payments Sunshine Act requires certain 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 CMS information related to payments or transfers of value made to physicians and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members.

Analogous State and Foreign Laws. Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, and are generally broad and are enforced by many different federal and state agencies as well as through private actions. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that any business arrangements we have with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm, and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the European Union. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of European Union Member States, such as the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could have a material adverse effect on our business, financial condition or results of operations.

The collection, use, disclosure, transfer or other processing of personal data, including personal health data, of individuals in the European Union is governed by the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018. It imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data; obtaining consent of individuals; providing notice to individuals regarding data processing activities; responding to data subject requests; taking certain measures when engaging third-party processors; notifying data subjects and regulators of data breaches; and implementing safeguards to protect the security and confidentiality of personal data. The GDPR imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States. Failure to comply with the requirements of the GDPR may result in fines of up to 20 million euros or four percent of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages. The GDPR increases our responsibility and potential liability in relation to personal data that we process, and we may be required to change our business practices or put in place additional mechanisms ensuring compliance with the GDPR. This may be onerous and adversely affect our business, financial condition, results of operations and prospects, and despite our efforts, there is a risk that we may be subject to fines, litigation and reputational harm in connection with our European activities.

Similar actions are either in place or under way in the United States. There are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act, or the CCPA, which went into effect on January

1, 2020, is creating similar risks and obligations as those created by GDPR, though the CCPA does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the United States and require us to develop and implement costly compliance programs.

If we further expand our operations outside the United States, we will need to dedicate additional resources to comply with U.S. laws regarding international operations and the laws and regulations in each jurisdiction in which we operate and plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

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

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

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from workplace and other work-related accidents, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

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

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

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

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

Our computer systems, as well as those of our CROs and other third-party contractors and consultants, are vulnerable to damage from computer viruses, unauthorized access, natural disasters (including hurricanes), 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 of our business and development programs. For example, the loss of preclinical studies or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce data. To the extent 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 also incur liability and the development of nalbuphine ER or any future product candidate could be significantly delayed.

In the ordinary course of our business, we directly or indirectly collect and store sensitive data, including intellectual property, confidential information, preclinical and clinical trial data, proprietary business information, personal data and personally identifiable health information of our clinical trial patients and employees, in our data centers and on our networks, or on those of third parties. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or internal bad actors, or breached due to employee error, a technical vulnerability, malfeasance or other disruptions. Although, to our knowledge, we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information and significant regulatory penalties, and such an event could disrupt our operations, damage our reputation, and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay our clinical development of our product candidates.

Risks Related to Employee Matters and Managing our Growth

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

We are highly dependent on Jennifer Good, our President and Chief Executive Officer; Thomas Sciascia, M.D., our Chief Medical Officer; and Helena Brett-Smith, M.D., our Chief Development Officer; as well as the other principal members of our management and scientific teams. Although we have formal employment agreements with Ms. Good and Dr. Sciascia, these agreements do not prevent them from terminating their employment with us at any time. Except as otherwise required by law, and except with respect to Yann Mazabraud, our Chief Commercial Officer and Head of International, whose employment agreement provides for a three-month termination notice period, all of the members of our executive team are employed "at will," meaning that they may terminate their employment with us at any time with or without notice and for any reason or no reason. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified scientific, clinical, manufacturing and sales and marketing personnel. Our industry has experienced a high rate of turnover of such personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key employees 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.

We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize nalbuphine ER or any future product candidate will be limited.

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

As of March 31, 2020 we had 19 employees. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development and regulatory affairs. In addition, if any product candidate appears likely to receive marketing approval, we expect to significantly expand our sales, marketing and distribution capabilities to support the potential commercialization of the product candidate. Our management may need to devote a significant amount of its attention to managing these growth activities. 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, retain key employees or identify, recruit and train additional qualified personnel. Our inability to manage the expansion of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of nalbuphine ER for additional indications or the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of any product candidate.

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

We are exposed to the risk that our employees, independent contractors and consultants may engage in fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, to provide accurate information to the FDA or comparable non-U.S. regulatory authorities, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, to report financial information or data accurately or to disclose unauthorized activities to us. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm and requirements to curtail or restructure our operations.

Risks Related to Our Common Stock

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

Our shares of common stock began trading on the Nasdaq Global Market on May 7, 2019. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares will not be sustained, which could put downward pressure on the market price for our common stock and thereby affect the ability of our stockholders to sell their shares. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

The trading price of our common stock is highly volatile, which could result in substantial losses for purchasers of our common stock.

The trading price of our common stock is highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The trading price for our common stock may be influenced by many factors, including:

- the timing and results of clinical trials of nalbuphine ER or any future product candidates;
- the success of existing or new competitive products or technologies;
- regulatory actions with respect to nalbuphine ER or any future product candidates or competitors' products and product candidates;

- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property rights;
- recruitment or departure of key personnel;
- expenses related to any of our development programs;
- results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimated financial results or development timelines;
- announcements or expectations of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- expiration of market stand-off or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- recommendations and changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems in the United States and other countries;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions, including recent adverse changes in the domestic and international financial markets, and the impacts of the COVID-19 pandemic; and
- other factors and considerations described in this “Risk Factors” section.

In addition, the novel coronavirus has been spreading rapidly around the world since December 2019 and has negatively affected the stock market and investor sentiment. The price and volatility of our common stock may be disproportionately affected as investors may favor traditional profit-making industries and companies during the times of market uncertainty and instability.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against public companies following declines in the trading prices of their securities. This risk is especially relevant for us because companies in the life sciences space have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and our resources, which could harm our business.

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

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

Future sales of shares of our common stock, including by us, employees and significant stockholders, could negatively affect our stock price.

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

All of our outstanding shares of common stock may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended, or the Securities Act, or to the extent that such shares have already been registered under the Securities Act and are held by non-affiliates of ours.

Moreover, holders of a substantial number of shares of our common stock have rights, subject to specified limitations and conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

In addition, we have registered all shares of common stock that we may issue under our equity compensation plans. These shares can be freely sold in the public market upon issuance and once vested, subject to volume limitations applicable to affiliates. If these additional shares are sold, or if it is perceived in the market that they will be sold, in the public market, the trading price of our common stock could decline.

Ownership of our common stock is concentrated among our executive officers and directors and their affiliates and our significant stockholders, who have significant influence over our business, which may prevent new investors from influencing significant corporate decisions.

Our executive officers and directors and their affiliates and our significant stockholders in the aggregate, beneficially own shares representing approximately 73.2% of our common stock as of May 7, 2020. As a result, our executive officers and directors and their affiliates and our significant stockholders acting together would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. This concentration of ownership control may:

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

Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below our initial public offering price and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other stockholders.

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

We have never declared or paid cash dividends on our capital stock and we do not intend to do so in the foreseeable future. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our product pipeline and business. In addition, the terms of any future debt financing that we may obtain may also preclude us from declaring and paying dividends. As a result, future appreciation, if any, in the market value of our common stock will be your sole source of gain for the foreseeable future. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it.

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

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company for up to five years. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements, and not being required to hold a nonbinding advisory

vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of SOX Section 404 and reduced disclosure obligations regarding executive compensation. If some investors find our common stock less attractive as a result of our reliance on these exemptions, the trading market for our common stock may be less active and our stock price may be more volatile.

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

As a public company, and particularly after we are no longer an "emerging growth company" or a "smaller reporting company," we will incur significant legal, accounting, investor relations and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Stock Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We may need to hire additional accounting, finance and other personnel in connection with our efforts to comply with the requirements of being a public company and our management and other personnel will need to devote a substantial amount of time in complying with these requirements, which could negatively impact our financial results. Current and changing laws, rules and regulations relating to corporate governance and public disclosure may increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, the rules and regulations applicable to us as a public company have made it, and we expect that they may continue to make it, more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. We are evaluating these rules and regulations and cannot currently predict or estimate the additional costs we may incur or the timing of such costs. In addition, these laws, rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, rules and regulations, 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, rules and regulations, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

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, or the Exchange Act, the Sarbanes-Oxley Act of 2002 and the rules and regulations of the Nasdaq Stock Market. The Sarbanes-Oxley Act of 2002 requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. Pursuant to SOX Section 404, we will be required to furnish a report by our management on our internal control over financial reporting beginning with our Annual Report on Form 10-K for our fiscal year ending December 31, 2020. However, while we remain an emerging growth company or a smaller reporting company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with SOX Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. We have never been required to test our internal control within a specified period and despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective. If we are unable to comply with the requirements of SOX Section 404 in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the trading price of our common stock could decline and we could be subject to sanctions or investigations by the Nasdaq Stock Market, the SEC or other regulatory authorities.

Members of our management team have limited experience managing a public company.

Members of our management team have limited experience managing a publicly traded company, interacting with public company investors and complying with the increasingly complex laws pertaining to public companies. Our management team may not successfully or efficiently manage our transition to being a public company subject to significant regulatory oversight and reporting obligations under the federal securities laws and the scrutiny of securities analysts and investors. These new obligations and constituents will require significant attention from our management team and could divert their attention away from the daily management of our business, which could materially adversely affect our business, financial condition and operating results.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2019, we had federal and state net operating loss carryforwards of $106.8 million, and federal research and development tax credit carryforwards of $3.2 million, which if not utilized generally will begin to expire in 2031 and 2032, respectively. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In general, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, a corporation that undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three year period, is subject to limitations on its ability to utilize its pre-change net operating losses and research and development tax credit carryforwards to offset future taxable income. Due to our Series A convertible preferred stock financing in December 2012 and the shares issued in connection with our IPO in May 2019, an "ownership change" under Section 382 of the Code occurred. As a result, our ability to use approximately $91.3 million of our net operating loss carryforwards and approximately $3.0 million of our research and development tax credits is limited. We may experience further ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If a further ownership change occurs, our ability to use our net operating loss carryforwards might be further limited. We have not conducted a detailed study to document whether our historical activities qualify to support our research and development credit carryforwards. A detailed study could result in adjustment to our research and development credit carryforwards. If we determine that an ownership change occurs and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development tax credit carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

There is also a risk that due to regulatory changes, such as suspensions on the use of net operating losses, or other unforeseen reasons, our existing net operating losses could expire or otherwise become unavailable to offset future income tax liabilities. As described below in "Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the Tax Cuts and Jobs Act, or the Tax Act, as amended by the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, includes changes to U.S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. In addition, state net operating losses generated in one state cannot be used to offset income generated in another state. For these reasons, even if we attain profitability, we may be unable to use a material portion of our net operating losses and other tax attributes.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Recent changes in tax law may adversely affect our business or financial condition. On December 22, 2017, the U.S. government enacted the Tax Act, which significantly reformed the Code. The Tax Act, among other things, contained significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for net operating losses arising in taxable years beginning after December 31, 2017 to 80% of current year taxable income and elimination of net operating loss carrybacks for losses arising in taxable years ending after December 31, 2017 (though any such NOLs may be carried forward indefinitely), the imposition of a one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time, and the modification or repeal of many business deductions and credits.

As part of Congress's response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, and the CARES Act was enacted on March 27, 2020. Both contain numerous tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application of the 80%-of-income limitation on the use of net operating losses, which was enacted as part of the Tax Act. It also provides that net operating losses arising in any taxable year beginning after December 31, 2017, and before January 1, 2021 are generally eligible to be carried back up to five years. The CARES Act also temporarily (for taxable years beginning in 2019 or 2020) relaxes the limitation of the tax deductibility for net interest expense by increasing the limitation from 30 to 50% of adjusted taxable income.

Regulatory guidance under the Tax Act, the FFCR Act and the CARES Act is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. It is also likely that Congress will enact additional legislation in connection with the COVID-19 pandemic, some of which could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the FFCR Act or the CARES Act.

Provisions in our organizational documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

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

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

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits an “interested stockholder,” which is either a person who owns at least 15% of our outstanding voting stock or an affiliate or associate who owned at least 15% of our outstanding voting stock at any time within the prior three years, from engaging in a business combination with us for a period of three years after the date of the transaction in which the person became an “interested stockholder” unless the business combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This 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.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders and that the federal district courts of the United States of America are the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. These choice of forum provisions could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of fiduciary duty owed by any director, officer, other employee or stockholder of our company to us or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law or as to which the Delaware General Corporation Law confers jurisdiction on the Court of Chancery or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or by-laws or governed by the internal affairs doctrine. Our certificate of incorporation further provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Neither of these choice of forum provisions would affect suits brought to enforce any liability or duty created by the Exchange Act or the rules and regulations thereunder, jurisdiction over which is exclusively vested by statute in the United States federal courts or any other claim for which United States federal courts have exclusive jurisdiction.

These choice of forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provisions contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could materially adversely affect our business, financial condition and operating results.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.

Unregistered Sales of Equity Securities

We did not sell or issue any equity securities during the three months ended March 31, 2020 that were not registered under the Securities Act of 1933, as amended, or the Securities Act.

Use of Proceeds from Registered Securities

On May 9, 2019, we closed our initial public offering, or IPO, in which we issued and sold 5,500,000 shares of common stock at a public offering price of $10.00 per share. The aggregate gross proceeds to us from our IPO offering were $55.0 million.

All of the shares of common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (Registration No. 333-230745), which was declared effective by the SEC on May 7, 2019. The aggregate net proceeds to us from the IPO were approximately $48.2 million, after deducting underwriting discounts and commissions and offering expenses payable by us of approximately $6.8 million.

No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

As of March 31, 2020, we had not used any of the net proceeds from the IPO. There has been no material change in our planned use of the net proceeds from the IPO as described in our final prospectus for the IPO filed with the SEC pursuant to Rule 424(b) under the Securities Act. We have invested the net proceeds from the IPO in money market funds.

Item 6. Exhibits.

Exhibit Number	Description
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) or 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) or 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed herewith.

SIGNATURES

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

TREVI THERAPEUTICS, INC.

Date: May 7, 2020

By: /s/ Christopher Seiter

Christopher Seiter

Chief Financial Officer
(Principal Financial Officer)

Exhibit 31.1

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Jennifer L. Good, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) 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

c) 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: May 7, 2020

By: /s/ Jennifer L. Good
Jennifer L. Good
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Christopher Seiter, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) 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

c) 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: May 7, 2020

By: /s/ Christopher Seiter
Christopher Seiter
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc. (the "Company") for the period ended March 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jennifer L. Good, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to her knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: May 7, 2020

By: /s/ Jennifer L. Good
Jennifer L. Good
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc. (the "Company") for the period ended March 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Christopher Seiter, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: May 7, 2020

By: /s/ Christopher Seiter
Christopher Seiter
Chief Financial Officer
(Principal Financial Officer)