UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2019

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 FOR THE TRANSITION PERIOD FROM TO**

Commission File Number 001-38886

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)**

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

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**

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

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

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

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

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

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

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

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

As of June 28, 2019, the last business day of the Registrant's most recently completed second fiscal quarter, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the shares of common stock on The Nasdaq Stock Market, was $29.0 million.

The number of shares of Registrant's Common Stock outstanding as of March 13, 2020 was 17,834,570.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Proxy Statement for the registrant's 2020 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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PART I

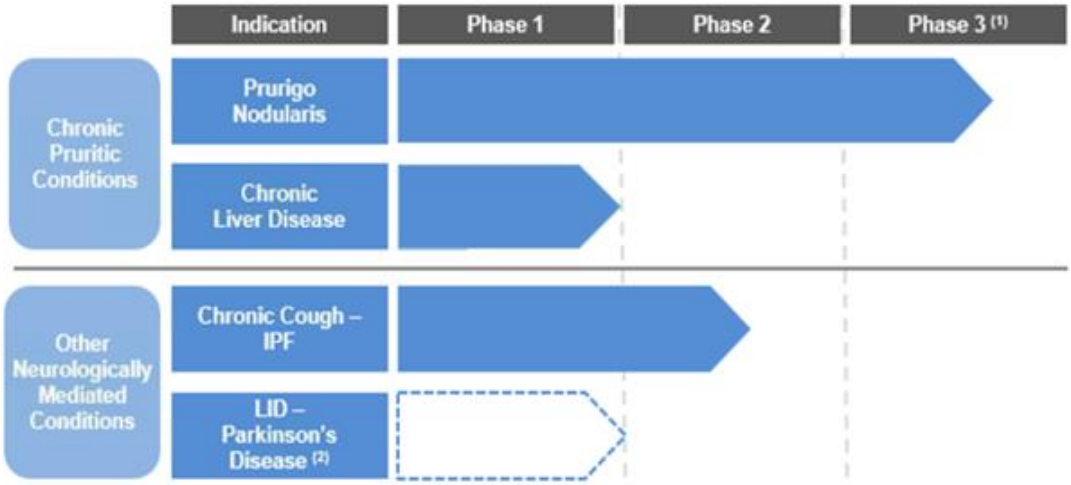
Item 1. Business.

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. 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, we believe it has the potential to be effective in treating each of these conditions. We are currently 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, and expect to report top-line data from the trial in the second half of 2020. If successful, we expect that we will use the PRISM trial and an additional Phase 3 clinical trial that we plan to conduct to support the submission of a new drug application, or NDA, to the United States Food and Drug Administration, or FDA, and a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis.

Nalbuphine ER is an oral extended release formulation of nalbuphine. Nalbuphine is a mixed k-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 k- 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.

The following table summarizes key information about our active clinical programs for nalbuphine ER. We have retained worldwide development and commercial rights for nalbuphine ER in all indications.



(1) Our prurigo nodularis program consists of our ongoing Phase 2b/3 clinical trial and an additional Phase 3 clinical trial that we plan to conduct.

(2) The dotted line segment indicates that we have not yet commenced any clinical trials for our LID program. The planned trials will be subject to regulatory input.

Chronic pruritus, defined as itching lasting longer than six weeks, causes a number of physical and psychological issues that can substantially impact patients' daily well-being. The urge to scratch can be unbearable and the act of scratching can remove layers of skin and break the skin barrier, leading to bleeding and scarring and greatly increasing the risk of infection. Chronic pruritus can also lead to trouble sleeping, resulting in loss of work productivity and increased anxiety and depression as patients struggle to maintain self-control. Chronic pruritus is a hallmark of many dermatologic and systemic diseases and is the predominant reason that patients with these diseases experience so much discomfort. A recent report published in the Journal of the American Academy of Dermatology estimated that up to 26% of the worldwide population will suffer from chronic pruritus at some point in their lives. According to the Global Pruritus Therapeutic Market Research Report issued in 2017, the market for pruritus therapeutics was $10.8 billion in 2016 and is expected to grow to $14.3 billion in 2022. Despite the large market opportunity and the severity of chronic pruritus, there are no drugs approved in the United States or Europe for the treatment of moderate to severe pruritus. Nalbuphine ER's dual mechanism of action targets opioid receptors located in both the central and peripheral nervous systems, each of which plays a role in modulating the sensation of itch. We believe this makes nalbuphine ER a promising potential therapy for the treatment of chronic pruritus.

We have completed clinical trials in two distinct and serious pruritic conditions, uremic pruritus and pruritus associated with prurigo nodularis, with over 400 patients treated with different doses of nalbuphine ER in these trials. Uremic pruritus is a pruritic condition occurring in patients with chronic kidney disease typically receiving dialysis. Prurigo nodularis is an intensely pruritic dermatologic condition characterized by the presence of nodular pruriginous lesions such as papules or plaques. Among other endpoints, these trials measured the reduction in pruritus as reported on the worst itch numerical rating scale, or WI-NRS, 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.

In our Phase 2b/3 clinical trial in uremic pruritus, we enrolled 373 patients with moderate to severe uremic pruritus. Patients were randomized to one of three arms: either 108 mg or 54 mg of nalbuphine ER or placebo, each administered twice daily. The primary endpoint in the trial was the change from baseline in patients' seven-day mean WI-NRS scores. The trial met its primary endpoint in the 108 mg arm, where patients reported a mean 3.49 point reduction in WI-NRS score from baseline to week eight as compared with a mean 2.80 point reduction in the placebo arm (p=0.017). Patients in the 54 mg arm reported a mean 3.10 point reduction in WI-NRS score from baseline, which was larger than the 2.80 point reduction in the placebo arm, although the difference was not statistically significant (p=0.441). The reduction in WI-NRS scores across the three arms of the trial demonstrated a dose response. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of less than 0.05 is generally considered to represent statistical significance, meaning that there is a less than five percent likelihood that the observed results occurred by chance.

In our Phase 2 clinical trial in prurigo nodularis, we enrolled 63 patients with prurigo nodularis who had moderate to severe pruritus. Patients were randomized to one of three arms: either 162 mg or 81 mg of nalbuphine ER or placebo, each administered twice daily. The primary endpoint of the trial was the proportion of patients reporting at least a 30% reduction from baseline to week 10 in seven-day mean WI-NRS scores, patients who were defined as responders. In the 162 mg arm, patients reported a mean 2.51 point reduction in WI-NRS score from baseline as compared with a mean 1.75 point reduction in the placebo arm (p=0.083), with 44% of the patients in the 162 mg arm constituting responders as compared to 36% of the patients in the placebo arm (p=0.323). In the 81 mg arm, patients reported a mean 2.14 point reduction in WI-NRS score from baseline, with 27% of the patients in the arm constituting responders (p=0.779). A key secondary endpoint of the trial was the proportion of patients reporting at least a 50% reduction in WI-NRS score from baseline. In the 162 mg arm, 33% of patients reported at least a 50% reduction in WI-NRS score as compared to 18% of patients in the placebo arm (p=0.083). The trial met a key secondary efficacy endpoint, reduction of ItchyQoL™ scores, in the 162 mg arm compared to the placebo arm (p=0.022). ItchyQoL measures quality of life improvements from pruritus reduction. The secondary endpoints of the trial were not powered for statistical significance.

We conducted a *post hoc* analysis of the data from the 50 patients who completed the 10-week course of treatment in our Phase 2 clinical trial in prurigo nodularis. With the small number of patients enrolled in the trial, the number of patients discontinuing treatment prior to the end of the trial had a substantial impact on the results. Approximately 75% of the discontinuations in the nalbuphine ER arms occurred in an initial two-week titration period among patients who had not reached the target dose of nalbuphine ER. As a result, we believe that an analysis of the trial results in this subset of patients, whom we refer to as completers, provides informative data

regarding nalbuphine ER because it eliminates the effects of patient discontinuations. In the trial, 50% of the completers in the 162 mg arm reported at least a 50% reduction in WI-NRS score from baseline, as compared to 20% of the completers in the placebo arm (p=0.028), although this analysis was not powered for statistical significance. As the patients in the 162 mg arm had a mean baseline WI-NRS score of 8.05, a 50% reduction in WI-NRS score from baseline for patients in this arm was comparable to a 4-point reduction in WI-NRS score, the primary efficacy endpoint of our PRISM trial.

Based on the results of our prurigo nodularis and uremic pruritus trials and open label extension trials in both indications, and discussions with the FDA and European regulatory authorities, in September 2018, we initiated our Phase 2b/3 Pruritus Relief through Itch Scratch Modulation, or PRISM, trial of nalbuphine ER 162 mg tablets in patients with severe pruritus associated with prurigo nodularis. We plan to conduct the trial at approximately 60 sites in the United States and Europe. To date, we have enrolled approximately 45% of the target number of patients.

The PRISM trial consists of two parts. The first part of the trial is a randomized, double-blind, placebo-controlled, parallel, two-arm, 14-week treatment study that is evaluating the safety and anti-pruritic efficacy of nalbuphine ER 162 mg tablets. The second part of the trial is an open label extension to evaluate nalbuphine ER's long-term safety profile as well as its effects on key prurigo nodularis parameters, including itch and skin healing, over a further 38 weeks, resulting in a 52-week overall treatment period. The trial is designed to be conducted in 240 patients. However, under the protocol for the trial, once 50% of the patients are evaluable for the primary efficacy endpoint, an unblinded statistician for the trial will review the available data, perform a sample size re-estimation and advise us on whether we should increase the size of the trial. We expect to reach 50% patient enrollment during the second quarter of 2020. Once all of these patients complete the primary efficacy endpoint, the sample size re-estimation analysis will occur. We expect this analysis will occur in mid-2020. Depending on the results of the sample size re-estimation, the trial may be increased to up to 360 patients. The primary efficacy endpoint for the 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. The trial also includes several secondary endpoints, including mean changes from baseline to week 14 in skin healing assessments and quality of life measurements, such as ItchyQoL. In designing the statistical plan for the trial, we considered the rates of patient discontinuations we experienced in our earlier trials. We believe that these discontinuation rates can be reduced through increased patient and physician education prior to the commencement of dosing. We expect to report top-line data from the 14-week blinded treatment period of the PRISM trial in the second half of 2020. We will need to conduct an additional Phase 3 clinical trial to support the submission of an NDA to the FDA and an MAA to the EMA. We may initiate this trial before the PRISM trial is complete.

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 trial in patients with mild, moderate and severe hepatic impairment. In the single ascending dosing portion of this trial in patients with mild and moderate hepatic impairment, which we completed, there were no serious adverse events reported. 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 this trial to support an NDA submission for nalbuphine ER for pruritus in prurigo nodularis.

We are not actively developing nalbuphine ER for uremic pruritus at this time based on our evaluation of the market dynamics, but may consider resuming development in the future.

As a result of nalbuphine's ability to modulate the k- and μ-opioid receptors, which are known to be involved in the pathophysiology of chronic cough in patients with IPF and in LID in patients with Parkinson's disease, we are also pursuing the development of nalbuphine ER for each of these indications. We are conducting a Phase 2 clinical trial of nalbuphine ER to evaluate the safety of nalbuphine ER in patients with IPF, and make an initial assessment of its efficacy on cough, with data expected in the second half of 2020. We have written the protocol for a Phase 2 clinical trial to evaluate the effect of nalbuphine ER on LID in patients with Parkinson's disease and plan to submit an investigational new drug, or IND, application 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.

Our Strategy

We are focused on the development and commercialization of nalbuphine ER to treat serious neurologically mediated conditions. The key elements of our strategy are:

- ***Complete the clinical development of nalbuphine ER for the treatment of pruritus associated with prurigo nodularis.*** We are conducting our PRISM trial to evaluate the safety and anti-pruritic efficacy of nalbuphine ER in patients with severe pruritus associated with prurigo nodularis. We expect to report top-line data from the blinded treatment period of the trial in the second half of 2020. In addition, the protocol for the PRISM trial provides for a sample size re-estimation analysis once 50% of the patients in the trial are evaluable for the primary endpoint. We expect the re-estimation analysis will occur in mid-2020. We will need to conduct an additional Phase 3 clinical trial to support the submission of an NDA to the FDA and an MAA to the EMA.
- ***Pursue continued development of nalbuphine ER for additional pruritic conditions.*** Based on the proof of concept data in pruritus from our clinical trials in patients with prurigo nodularis and uremic pruritus, we plan to continue to develop nalbuphine ER for the treatment of other pruritic conditions. We are conducting a Phase 1b clinical trial in patients with chronic liver disease to evaluate the safety and PK of nalbuphine ER in these patients. 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 on nalbuphine ER in potential future safety and efficacy studies in patients with relevant liver diseases. We intend to start planning a Phase 2 trial of nalbuphine ER in patients with pruritus associated with PBC. We may also seek to develop nalbuphine ER for the treatment of pruritus associated with additional dermatology, oncology, hematology and neurology related conditions.
- ***Leverage the dual mechanism of action of nalbuphine ER to pursue other neurologically mediated conditions.*** We intend to develop nalbuphine ER to treat other serious neurologically mediated conditions that share a common pathophysiology mediated through opioid receptors in the central and peripheral nervous systems. We are conducting a Phase 2 clinical trial to evaluate the safety of nalbuphine ER in patients with IPF, and make an initial assessment of its efficacy on cough, with data expected in the second half of 2020. We have written the protocol for a Phase 2 clinical trial to evaluate the effect of nalbuphine ER on LID in patients with Parkinson's disease and plan to submit an IND application in the upcoming months.
- ***Maximize the commercial potential of nalbuphine ER.*** We have retained worldwide commercial rights for nalbuphine ER. If nalbuphine ER receives marketing approval from the FDA for any of the indications we are currently pursuing, we plan to commercialize nalbuphine ER in the United States with our own focused, specialty sales organization targeting the physicians specializing in these conditions. If nalbuphine ER receives marketing approval for any of these indications outside the United States, we expect to utilize a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize nalbuphine ER in such markets.
- ***Evaluate business development opportunities and potential collaborations.*** We plan to evaluate the merits of entering into collaboration agreements with other pharmaceutical or biotechnology companies that may contribute to our ability to efficiently advance product candidates, build our product pipeline and concurrently advance a range of research and development programs.

Nalbuphine Mechanistic Rationale

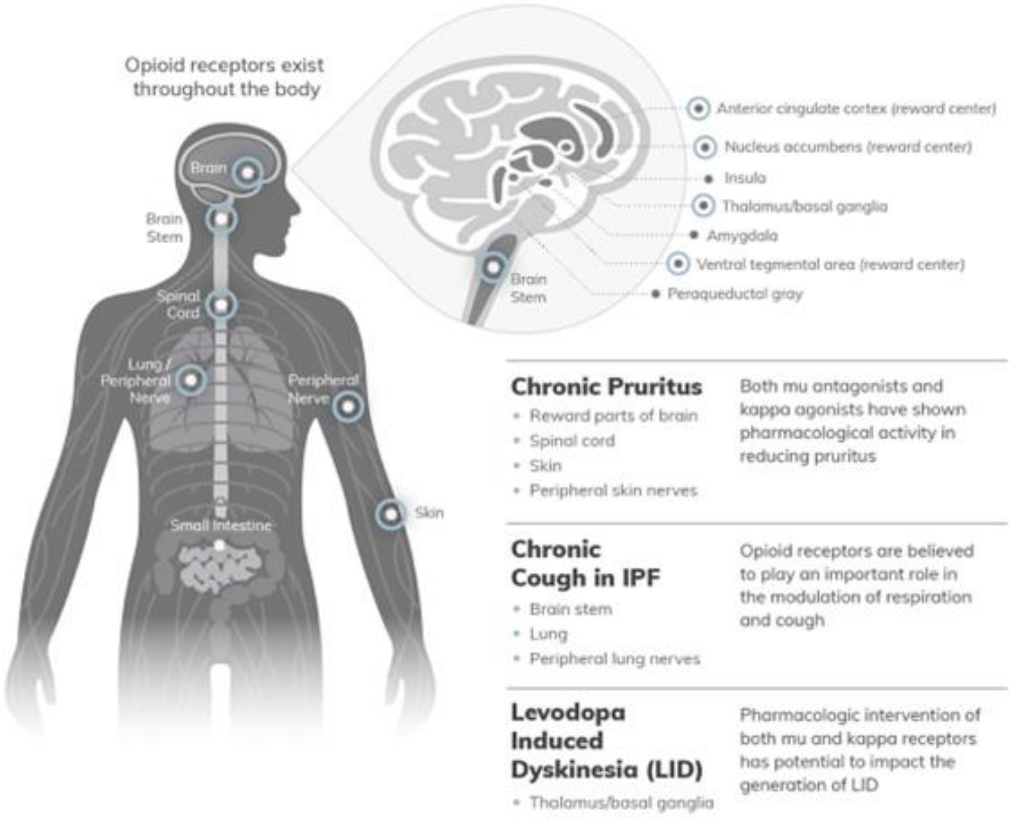
Nalbuphine is a mixed k-opioid receptor agonist and µ-opioid receptor antagonist. Drugs targeting opioid receptors have been studied for decades and the biology and pharmacology of these receptors are well-understood. There are three types of opioid receptors, mu ("µ"), kappa ("k") and delta ("δ"), which are expressed in varying concentrations in many different tissues, including the central and peripheral nervous systems, airway and lung tissue, circulating immune and inflammatory cells and the skin.

Modulation of opioid receptors, either naturally or with opioid drugs, results in multiple signaling actions at the cellular level. The receptor dynamics are complex and receptor signaling differs depending on whether the receptor is being exposed to an agonist or antagonist opioid drug. Agonists activate the receptors to which they bind, and antagonists bind to receptors, and can block the activity of agonists. In addition, opioid drugs of the same class may have different effects depending on their pharmacological properties.

In addition to the individual cellular dynamics, published research also supports the phenomena of network interaction dynamics, where activation of one type of opioid receptor type at one anatomical location can influence the activity of a different type of opiate receptor located at a different anatomical location. For example, published research has shown evidence of signaling between cell groups where k-receptor activation on specific cells can antagonize µ-opioid receptor activation on other cells. As a result of these apparent network interaction dynamics between the k- and µ-opioid receptors, we believe that simultaneously modulating both k- and µ-opioid receptors with a single drug offers significant therapeutic potential in diseases that are mediated through these receptors.

Published research suggests that in certain diseases the concentration and expression of opioid receptors is different for people with the disease as compared to healthy individuals. For example, published research has shown that human skin tissue samples from patients with prurigo nodularis show a down regulation of µ-opioid receptor expression as compared to normal skin. In patients with Parkinson's disease, multiple published studies have shown a reduction in opioid receptor density in the thalamus and basal ganglia regions of the brain in patients suffering from LID as compared to patients not suffering from dyskinesia. We believe these differences in opioid receptor concentration and expression between healthy individuals and people with disease suggest that opioid drugs targeting these receptors have the potential to offer therapeutic benefit to people suffering from these diseases.

As shown in the diagram below, k- and µ-opioid receptors are naturally concentrated in several areas of the body, including in the brain, brain stem, spinal cord, peripheral nerves, lungs and skin, which are the areas of the body involved in the physiology of chronic pruritus, chronic cough in IPF and LID.



With respect to pruritus, the sensation of itch and the urge to scratch are known to be mediated by k- and µ-opioid receptor expression in the reward centers of the brain as well as the spinal cord, skin and peripheral nervous system. Published clinical trials of the µ-agonist nalfurafine have demonstrated effectiveness in reducing uremic pruritus and pruritus secondary to chronic hepatic disease. Nalfurafine is approved and marketed in Japan for both conditions. In addition, a number of published clinical trials have reported on the effectiveness of the µ-antagonist naltrexone in reducing pruritus related to hepatic disease and pruritus related to prurigo nodularis.

With respect to cough, k- and µ-opioid receptors in the brain stem, lungs and the peripheral lung nerves are believed to be involved in mediating respiration and the cough reflex. While there are no approved opioid therapeutics for suppression of cough in humans, µ-agonist opioids have been used to suppress cough. In addition, the mixed k-agonist and µ-partial agonist butorphanol is approved and marketed for animals in a veterinary injection and tablet formulation for the relief of chronic non-productive cough and has been found to be 15 to 20 times more active in suppressing cough than either codeine or dextromethorphan. Further, in clinical trials both butorphanol and pentazocine, a mixed k-agonist and µ-antagonist, have demonstrated suppression of cough in fentanyl-induced cough during anesthetic induction in patients.

With respect to Parkinson's disease, it is believed that opioid signaling in the thalamus and basal ganglia regions of the brain may play a role in mediating LID. Published research using a brain imaging technique has shown that Parkinson's patients suffering from LID have reduced opioid receptor availability in the thalamus and the basal ganglia, as compared to Parkinson's patients responding normally to levodopa therapy and not exhibiting LID. Additionally, there is an inverse correlation between the availability of these receptors and the severity of dyskinesia. This decrease in opioid receptor availability is believed to be due to heightened opioid transmission in these brain regions in patients with LID. In addition, a number of opioid components have been evaluated in preclinical animal models of LID and the data indicate that μ-antagonism has the most benefit, with k-agonism also having desirable effects.

Nalbuphine ER

Nalbuphine ER is an oral extended release formulation of nalbuphine, a small molecule and a member of the opioid agonist-antagonist class of drugs. Nalbuphine acts as an agonist at the opioid k-receptor while competitively antagonizing the μ-opioid receptor. Nalbuphine is a marketed drug currently available only as nalbuphine hydrochloride for injection, a generic equivalent to Nubain, which has been approved in the United States and Europe for use in the relief of moderate to severe pain for more than 20 years. Nalbuphine is not currently classified as a controlled substance in the United States or Europe and is not commercially available in an oral dosage form. We are developing nalbuphine ER to treat serious neurologically mediated conditions, including chronic pruritus, chronic cough in patients with IPF and LID in patients with Parkinson's disease.

We have leveraged the known mechanism and proven biological activity of nalbuphine in pain to expedite the clinical development of nalbuphine ER. We have also drawn on the safety and tolerability data from eight prior clinical trials of nalbuphine ER conducted by Penwest, from which we have licensed rights to nalbuphine ER, including two Phase 2 clinical trials of nalbuphine ER for the treatment of pain, to support our clinical development efforts. We believe that the established efficacy and safety profile of nalbuphine and the clinical experience with nalbuphine ER provide a strong foundation for advancing nalbuphine ER into late-stage clinical trials.

Our Nalbuphine ER Development Programs

Active Chronic Pruritus Programs

We are developing nalbuphine ER for the treatment of chronic pruritus associated with various conditions. We have filed an IND with the FDA covering nalbuphine ER in pruritus in prurigo nodularis and uremic pruritus. We have completed two double-blind, placebo-controlled clinical trials in patients with moderate to severe uremic pruritus and moderate to severe pruritus associated with prurigo nodularis that have established proof of concept in these indications. We believe that the pruritus associated with multiple distinct conditions, including prurigo nodularis, pruritus in relevant liver diseases such as PBC, and uremic pruritus, involves activation of a common neuronal pathway for itch signaling.

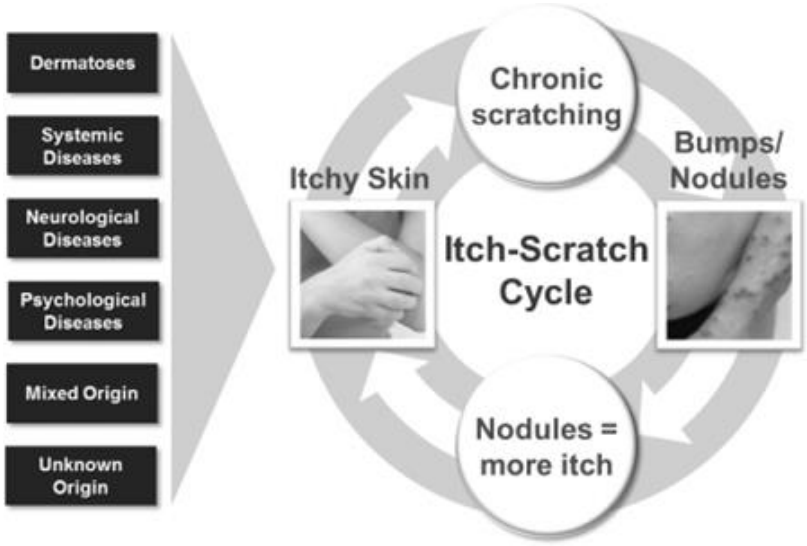
Chronic pruritus, defined as itching lasting longer than six weeks, causes a number of physical and psychological issues that can substantially impact patients' daily well-being. The urge to scratch can be unbearable, and the act of scratching can remove layers of skin and break the skin barrier leading to bleeding, scarring and greatly increasing the risk of infection. Chronic pruritus can also lead to trouble sleeping, resulting in loss of work productivity and increased anxiety and depression as patients struggle to maintain self-control. Chronic pruritus is a hallmark of many dermatologic and systemic diseases and is the predominant reason that patients with these diseases experience so much discomfort. A recent report published in the Journal of the American Academy of Dermatology estimated that up to 26% of the worldwide population will suffer from chronic pruritus at some point in their lives.

Despite its prevalence, chronic pruritus is not well addressed by current treatment options. Pruritic skin diseases are commonly treated with a multi-prong therapeutic approach. Skin barrier restoration and maintenance through application of topical moisturizers and treatment of skin lesions locally through the use of topical corticosteroids or other topical anti-inflammatory agents are the predominant first-line therapies for many pruritic skin diseases. Phototherapy and systemic immunomodulators, including biologics, are frequently used for more severe disease conditions. These treatment options may reduce pruritus to some degree in addition to their effects on skin health and inflammation. Yet many patients with chronic pruritus still report high levels of pruritus despite active topical or systemic therapy. This significant medical need is reflected by the widespread use of therapies intended to address pruritus specifically, such as oral antihistamines, despite evidence demonstrating their relative lack of efficacy, as well as concerns regarding their safety and tolerability. According to the Global Pruritus Therapeutic Market Research Report issued in 2017, the market for pruritus therapeutics was $10.8 billion in 2016 and is expected to grow to $14.3 billion in 2022.

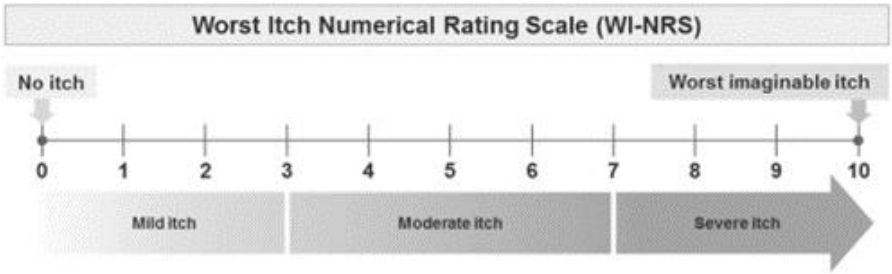
Prurigo Nodularis Program

Overview

Prurigo nodularis is an intensely pruritic dermatologic condition that constitutes a distinct dermatologic diagnosis. The core symptoms and criteria for diagnosis of prurigo nodularis are chronic pruritus, a history and/or signs of repeated scratching, and the presence of multiple pruriginous lesions. The presence and persistence of these pruriginous lesions are hallmarks of prurigo nodularis and aid in its diagnosis. These lesions are generally symmetrically distributed, intensely itchy papules, nodules or plaques, which may be associated with excoriations and ulcerations. As illustrated below, prurigo nodularis can arise from itch caused by a number of pre-existing conditions, with the initial scratching beginning a vicious itch-scratch cycle that results in the nodules that are characteristic of the distinct and separate disease of prurigo nodularis.



The pruritus associated with prurigo nodularis is generally considered to be one of the most severe and treatment-resistant forms of pruritus. In a retrospective study of 108 prurigo nodularis patients published in 2013 in the Journal of the European Academy of Dermatology and Venereology, patients rating their most severe itch over the prior 24 hours on the WI-NRS reported a median WI-NRS score of 8 and a mean and median duration of prurigo nodularis of 77.5 and 36 months, respectively. As illustrated in the diagram below, the WI-NRS 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, and scores of 7 or more are considered to indicate severe itch.



Patients with prurigo nodularis also typically experience a significant negative impact on their overall quality of life, including severe negative impacts on their confidence at work and in social activities. In a natural history study in 593 patients with prurigo nodularis at the Itch Center, University of Münster in Germany, it was shown that all of the patients in the study had a severe impairment of quality of life, as measured by the Dermatology Life Quality Index, or DLQI, a specific validated quality-of-life measurement that has been used in many different skin condition trials. With increasing intensity of pruritus, the quality of life worsened and DLQI values increased.

We believe that in 2016 there were approximately 250,000 prurigo nodularis patients in the United States and approximately 430,000 additional prurigo nodularis patients worldwide. No treatment for chronic pruritus associated with prurigo nodularis has been approved in the United States or Europe. Treatment of prurigo nodularis typically involves a multifaceted approach to treat the lesions and reduce pruritus. Therapies may include corticosteroids and other immunosuppressive or anti-inflammatory treatments, phototherapy and drugs such as gabapentin and Lyrica (pregabalin), prescription medicines approved for the treatment of seizures and neuropathic pain. Prurigo nodularis is often treatment-resistant with high recurrence rates.

Clinical Development

We have conducted a Phase 2 clinical trial and an open label extension study of nalbuphine ER in pruritus in patients with prurigo nodularis and are currently conducting our PRISM trial for nalbuphine ER for the treatment of pruritus associated with prurigo nodularis. If successful, we expect that we will use the PRISM trial and an additional Phase 3 clinical trial that we plan to conduct to support the submission of an NDA to the FDA and an MAA to the EMA. We may initiate this trial before the PRISM trial is complete.

Phase 2 Clinical Trial

We completed a Phase 2 clinical trial in August 2016 evaluating the safety and efficacy of nalbuphine ER as compared to placebo in patients with pruritus associated with prurigo nodularis. The trial was a multicenter, randomized, double-blind trial conducted at eight sites in the United States and Europe. The trial enrolled a total of 63 adult patients who had prurigo nodularis for at least six weeks and seven-day mean WI-NRS scores of at least 5, indicating moderate to severe pruritus. The patients were randomized across three treatment arms: either 162 mg or 81 mg of nalbuphine ER or placebo, each administered twice daily. The baseline seven-day mean WI-NRS scores for the three treatment arms were comparable: 8.05 for the 162 mg arm, 8.46 for the 81 mg arm and 7.96 for the placebo arm. There were three dosing periods in the trial, all of which were blinded: an initial two-week titration period during which patients received gradually increasing doses of nalbuphine ER or placebo, reaching the final assigned dose on day 15; an eight-week fixed dosing period; and a two-week off-treatment safety observation period.

The primary endpoint of the trial was the proportion of patients reporting at least a 30% reduction from baseline to week 10 in seven-day mean WI-NRS scores. We refer to these patients as 30% responders. Key secondary endpoints included:

- mean change in seven-day mean WI-NRS scores from baseline to week 10;
- the proportion of patients reporting at least a 50% reduction in seven-day mean WI-NRS score from baseline to week 10, whom we refer to as 50% responders, which reduction was comparable to a 4-point reduction in WI-NRS score, the primary efficacy endpoint for our PRISM trial, for patients in the 162 mg arm due to such patients having a mean baseline WI-NRS score of 8.05; and
- mean change from baseline to week 10 in total ItchyQoL score, a 22-question assessment using a severity scale of 1 to 5 that measures how pruritus affects patients' quality of life based on symptoms related to the pruritic condition, their functional limitations, their emotions and observations about their skin disease.

Efficacy Results

The following table summarizes the outcomes of the trial at week 10 for the primary endpoint and key secondary endpoints. The table below also includes results from a *post hoc* analysis of the 50 patients who completed the 10-week course of treatment, who we refer to as completers. We believe this *post hoc* analysis provides informative data as it eliminates the effects of patient discontinuations. With the small number of patients enrolled in the trial, the number of patients discontinuing treatment prior to the end of the trial had a substantial impact on the results, even though the number of discontinuations was small in absolute terms. Approximately 75% of the discontinuations in the nalbuphine ER arms occurred in the titration period among patients who had not reached the target dose of nalbuphine ER. During the trial, the discontinuation rate declined as enrollment progressed, which we believe was due to trial sites and investigators gaining experience with nalbuphine ER and the trial. We believe that these discontinuation rates can be reduced in future trials through increased patient and physician education prior to the commencement of dosing as the adverse events leading to these discontinuations were mild in nature and transient.

Endpoint	Nalbuphine ER 162 mg mITT(1): n=18 Completers(2): n=12	*p-value(3)*	Nalbuphine ER 81 mg mITT(1): n=22 Completers(2): n=18	*p-value(3)*	Placebo mITT(1): n=22 Completers(2): n=20
Responder Analyses					
30% responders in mITT population(4)	44%	p=0.323	27%	p=0.779	36%
Post hoc analysis of 30% responders in completer population	75%	p=0.026	33%	p=0.723	40%
50% responders in mITT population	33%	p=0.083	14%	p=0.981	18%
Post hoc analysis of 50% responders in completer population (comparable in 162 mg arm to a 4-point reduction in WI-NRS score)	50%	p=0.028	11%	p=0.649	20%

Endpoint	Nalbuphine ER 162 mg mITT(1): n=18 Completers(2): n=12	*p-value(3)*	Nalbuphine ER 81mg mITT(1): n=22 Completers(2): n=18	*p-value(3)*	Placebo mITT(1): n=22 Completers(2): n=20
Other Key Analyses					
Mean change in seven-day mean WI-NRS scores in mITT population	(2.51)	p=0.083	(2.14)	p=0.354	(1.75)
Post hoc analysis of mean change in seven-day mean WI-NRS scores in completer population	(3.43)	p=0.025	(2.52)	p=0.491	(1.85)
Mean change in total ItchyQoL score in mITT population	(13.83)	p=0.022	(7.79)	p=0.373	(5.45)

(1) Represents the modified intention to treat population, which consists of all of the patients who were randomized and commenced dosing.

(2) Consists of the patients who completed the 10-week course of treatment.
(3) All p-values compare treatment group to placebo. Only the primary endpoint was powered for statistical significance.
(4) Primary endpoint of the trial.

Safety Results

Nalbuphine ER was well tolerated in the trial. No serious adverse events, or SAEs, were assessed as definitely, probably or possibly related to nalbuphine ER. Two patients experienced SAEs that were assessed as unlikely to be related to nalbuphine ER, including one patient in the nalbuphine ER 81 mg arm of the trial whose SAEs occurred in connection with a car accident and one patient in the placebo arm with acute myeloid leukemia by bone marrow who experienced leukocytosis. The majority of treatment emergent adverse events, or TEAEs, occurred during the titration period. During the titration period, 73% of nalbuphine ER-treated patients experienced one or more adverse events, as compared to 46% of patients receiving placebo.

The following table summarizes the most common TEAEs experienced by patients in the trial, indicating the percentage of the modified intention to treat, or mITT, population of each arm that reported each such TEAE, subdivided by the grade of the reported TEAEs. Grade refers to the severity of the TEAE, with grade 1 TEAEs generally including mild or asymptomatic conditions or clinical or diagnostic observations only, grade 2 TEAEs generally including moderate events or minimal, local or noninvasive intervention events and grade 3 TEAEs generally including severe or medically significant events that are not immediately life-threatening, events requiring hospitalization or prolongation of hospitalization or disabling events. There were no grade 4 or grade 5 TEAEs reported in the trial, which would generally include life-threatening or urgent intervention events and deaths. Patients were able to report multiple TEAEs and, as a result, the percentages specified below for each arm or grade do not necessarily represent the percentage of patients in the arm that experienced any TEAE or any grade of any TEAE.

TEAE	Nalbuphine ER 162 mg (n=18)			Nalbuphine ER 81 mg (n=22)			Placebo (n=22)		
Grade	1	2	3	1	2	3	1	2	3
Dizziness	28%	11%	—	14%	9%	—	5%	—	—
Nausea	17%	22%	—	9%	9%	—	5%	—	—
Headache	11%	17%	—	9%	18%	—	5%	5%	—
Fatigue	11%	—	—	14%	5%	5%	—	—	—

Open Label Extension Study

We completed a one-year open label extension study of our Phase 2 clinical trial in patients with prurigo nodularis in July 2017. Patients who completed the Phase 2 clinical trial were able to enroll in the extension study following a safety washout period. Patients who enrolled in the extension study who had WI-NRS scores of at least 5 were immediately admitted to the active treatment period of the study. Patients with WI-NRS scores of less than 5 entered an observation period for up to 12 weeks. Patients in this observation period began to receive active treatment only following their first reported WI-NRS score of at least 5, or if they reached the end of the 12-week observation period and their WI-NRS scores remained below 5, they were required to leave the study.

Patients in the active treatment period received nalbuphine ER at a dose determined by self-titration (both up and down) to tolerance, ranging from 27 mg, once daily, up to 162 mg, twice daily, for up to 50 weeks. The variable-length observation period resulted in an active treatment period that could range from 38 to 50 weeks, depending on when the patient moved from the observation period to the active treatment period. The open label extension study enrolled 41 patients and of these 36 were admitted to the active treatment period. Of the patients admitted to the active treatment period, 20 patients completed at least 26 weeks of treatment and 16 patients completed 50 weeks of treatment, which are periods that correspond to guidelines of the International Council for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use to assess safety over periods of approximately six months and one year.

We observed mean changes in WI-NRS score from commencement of the active treatment period to week 26 and week 50 of -3.9 and -4.2, respectively, and a mean change in total ItchyQoL score from commencement of the active treatment period to week 26 and week 50 of -16.0 and -12.5, respectively. In the Verbal Rating Scale, a patient self-assessment of the presence and intensity of three distinct skin sensations (itching, burning and stinging) on a 5-category numeric assessment scale ranging from 0 to 4, over half of the patients reported at least a 1-category improvement from commencement of the active treatment period to their last observed study visit. In addition, we observed improvement at weeks 26 and 50 with respect to pruriginous lesions observed in Prurigo Activity Score, or PAS, assessments, which include physician assessments of skin lesions on a 0% to 100% scale, divided into five categories of 20% each, with respect to each of two parameters: percentage of excoriations/crusting and percentage of healed lesions. For the subsets of patients who completed 26 or 50 weeks of treatment and who had a PAS exam reported at both baseline and week 26 or 50, 13 of 19 patients at week 26, and 9 of 15 patients at week 50, showed at a least a 1-category improvement in excoriations/crusts; and 11 of 19 patients at week 26, and 7 of 15 patients at week 50, showed at least a 1-category improvement in healed lesions. We believe these data suggest that with continued longer-term treatment, both ongoing reduction in pruritus and improvement in the pruriginous lesions themselves may be observed in a meaningful proportion of patients.

Nalbuphine ER was well-tolerated in the open label extension study. The most frequent adverse events related to study drug were nausea and dizziness, which were reported in seven patients (19%) each, and fatigue, which was reported in six patients (17%). There were no treatment emergent SAEs reported that were considered related to study drug and the majority of adverse events were grade 1 or grade 2 in severity. There were no deaths reported in the study.

Ongoing PRISM Clinical Trial

Following completion of the Phase 2 clinical trial described above, we met with the FDA and European regulatory authorities to discuss the registration pathway for nalbuphine ER for pruritus associated with prurigo nodularis and the design of our Phase 2b/3 PRISM trial, including the target population, dose, duration and primary efficacy endpoint. Based on these discussions and the results of our prurigo nodularis and uremic pruritus trials, in September 2018 we initiated our Phase 2b/3 PRISM trial of nalbuphine ER 162 mg tablets in patients with severe pruritus associated with prurigo nodularis. We plan to conduct the trial at approximately 60 sites in the United States and Europe. To date, we have enrolled approximately 45% of the target number of patients. The pace of enrollment has been slower than anticipated primarily due to competition from other clinical trials and slower than planned site start-ups in Europe.

The PRISM trial consists of two parts. The first part of the trial is a randomized, double-blind, placebo-controlled, parallel, two-arm, 14-week treatment study that is evaluating the safety and anti-pruritic efficacy of nalbuphine ER 162 mg tablets. The second part of the trial is an open label extension to evaluate nalbuphine ER's long-term safety profile as well as its effects on key prurigo nodularis parameters, including itch and skin healing, over a further 38 weeks, resulting in a 52-week overall treatment period. The trial is designed to be conducted in 240 patients. However, under the protocol for the trial, once 50% of the patients are evaluable for the primary efficacy endpoint, an unblinded statistician for the trial will review the available data, perform a sample size re-estimation and advise us on whether we should increase the size of the trial. We expect to reach 50% patient enrollment during the second quarter of 2020. Once all of these patients complete the primary efficacy endpoint, the sample size re-estimation analysis will occur. We expect this analysis will occur in mid-2020. Depending on the results of the sample size re-estimation, the trial may be increased to up to 360 patients. If we increase the target number of patients in the trial as a result of the re-estimation analysis, the timing of our report of top-line data may be delayed. Eligible patients for this trial are adults with prurigo nodularis, defined by having at least ten pruriginous nodules, with predominantly nodular lesions overall, over at least two anatomically distinct body areas, with baseline seven-day mean WI-NRS scores of at least 7, indicating severe pruritus.

Patients will be dosed over two periods in the blinded portion of the trial: an initial two-week titration period during which patients receive gradually increasing doses of nalbuphine ER or placebo, reaching the final assigned dose on day 15, followed by a 12-week fixed-dosing period. Following the initial 14-week treatment period, patients will continue into another two-week blinded titration period during which patients from the placebo arm will cross over to active drug with a standard escalating titration schedule, while patients from the nalbuphine ER arm remain at a stable dose of 162 mg twice daily. This blinded two-week period will be followed by 36 weeks of stable dosing at 162 mg twice daily of open label nalbuphine ER for all participants. The open label extension will conclude with a final two-week off-treatment washout and safety observation period for all patients.

The primary efficacy endpoint for the 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. Key secondary endpoints include the mean changes from baseline to week 14 in WI-NRS and ItchyQoL scores and the difference in percentage of patients having a 1-category improvement in the percentage of pruriginous lesions with excoriations or crusts on the PAS at week 14. We expect to report top-line data from the 14-week blinded treatment period of the PRISM trial in the second half of 2020.

Next Steps

If the results of the PRISM trial and the additional Phase 3 clinical trial that we need to conduct are positive, and the data from the other required supportive trials are also favorable, we would plan to seek approval for nalbuphine ER for pruritus associated with prurigo nodularis by submitting to the FDA a Section 505(b)(2) New Drug Application, which would rely on the FDA's previous findings for the safety and effectiveness of nalbuphine, in addition to the data we generate regarding nalbuphine ER.

We have also obtained scientific guidance from regulatory authorities in two European countries, Sweden and Germany with respect to regulatory paths supporting submission of an MAA for pruritus associated with prurigo nodularis. We have also initiated development of a Pediatric Investigational Plan with European health authorities.

Pruritus in Chronic Liver Disease Program

Overview

Based upon nalbuphine ER's dual mechanism of action that targets k- and μ-opioid receptors and the anti-pruritic effect demonstrated in our clinical trials for the treatment of prurigo nodularis and uremic pruritus, we are developing nalbuphine ER for pruritus associated with chronic liver disease. This condition causes severe whole-body itch. It is an intense, intractable, debilitating condition that significantly disrupts patients' daily activities and sleep, and consequently impairs their quality of life. Pruritus tends to be the most common in cholestatic liver diseases, such as PBC and primary sclerosing cholangitis, or PSC. Chronic pruritus also occurs in connection with other liver diseases, including chronic hepatitis C.

According to a 2018 article published by the American Association for the Study of Liver Diseases, there were approximately 130,000 PBC patients in the United States in 2017. We estimate that the worldwide prevalence of PBC is between 2 and 40 per 100,000 persons and that the prevalence of pruritus in patients with PBC ranges between 37% and 55%. Based on this prevalence, we estimate that in 2017 there were 150,000 or more diagnosed patients with PBC and pruritus worldwide, including approximately 65,000 in the United States. We estimate that the prevalence of PSC is between 1 and 16 per 100,000 persons worldwide and there are 30,000 or more patients with PSC in the United States.

No treatment for pruritus associated with chronic liver disease has been approved in the United States or Europe, but nalfurafine (marketed as Remitch) is approved in Japan for pruritus associated with chronic liver disease. Treatment of pruritus associated with chronic liver disease may include off-label treatment with bile acid sequestrants, such as cholestyramine, which 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 may also include the antibiotic rifampicin, naltrexone, the anti-depressant sertraline, phototherapy and drugs such as gabapentin and Lyrica (pregabalin), prescription medicines approved for the treatment of seizures and neuropathic pain.

Clinical Development

We are conducting a Phase 1b clinical trial in patients with chronic liver disease to evaluate the safety and PK of nalbuphine ER in this population. This trial was designed as an open label, non-randomized, parallel-group, single and multiple ascending dose 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 PBC, a form of chronic liver disease.

Chronic Cough in Idiopathic Pulmonary Fibrosis Program

Idiopathic pulmonary fibrosis, or IPF, is a rare, chronic, progressive lung disease, characterized by scarring and thickening of lung tissue leading to an irreversible loss of lung function and reduced life expectancy. Most patients diagnosed with IPF suffer from a dry, non-productive chronic cough that interrupts their daily living and significantly contributes to poor quality of life. Chronic coughing can have a debilitating physical and psychosocial burden, exacerbate concomitant respiratory disease, cause loss of sleep and reduce mobility. Cough is an independent predictor of disease progression in IPF, and therefore we believe cough may contribute to the progression of the underlying disease.

Approximately 130,000 adults in the United States and 3 million adults worldwide are believed to have IPF. In addition, 70% to 85% of IPF patients are reported to suffer from chronic cough. These patients can cough over 50 times per hour, which can lead to other morbidities. There are no approved therapies for the treatment of chronic cough in patients suffering with IPF.

The opioid class of drugs has demonstrated the ability to suppress cough and is used in the clinical management of cough. There is also preclinical and clinical evidence that mixed agonist-antagonist drugs can also be effective in treating cough. We believe nalbuphine ER has the potential to be an effective treatment for chronic cough in patients with IPF. We are 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 diagnosed with IPF at approximately 12 sites in the United Kingdom Patients will be randomized into one of two treatment arms. The patients in the first treatment arm will receive nalbuphine ER for three weeks, which period will be followed by a two-week washout period and then a three-week treatment period during which they will receive placebo. The patients in the second treatment arm will receive placebo during the first three-week treatment period, and following a two-week washout period, will receive nalbuphine ER during the second three-week treatment period. During the active treatment periods, nalbuphine ER will be studied over a dosing range starting at 27 mg once daily and titrated in steps to 162 mg twice daily. The primary efficacy endpoint of the trial is mean percent change in daytime cough frequency as measured by a cough monitor as compared in the nalbuphine ER treatment periods and the placebo treatment periods. Secondary endpoints in the trial include assessments of fatigue, dyspnea or shortness of breath and cough severity. We expect to report top-line data from the trial in the second half of 2020.

Levodopa-Induced Dyskinesia in Parkinson's Disease

Parkinson's disease is a chronic neurodegenerative disorder that primarily affects motor function. Levodopa, which replaces lost dopamine, is considered the "gold standard" and the most effective therapy for Parkinson's disease. Over time, patients with Parkinson's disease require increasingly higher or more frequent doses of levodopa to avoid recurrent periods when levodopa therapy is ineffective, which are characterized by slowness of movement, rigidity, impaired walking, tremors, and postural instability, and during which the underlying symptoms of Parkinson's disease return. Extended treatment of Parkinson's disease with levodopa frequently results in dyskinesia, which is characterized by involuntary movements that are non-rhythmic, purposeless and unpredictable, negatively impacting patients' daily lives.

According to the Parkinson's Foundation, Parkinson's disease affects approximately one million patients in the United States and 10 million patients worldwide. Approximately 62% of Parkinson's disease patients in the United States are treated with levodopa, and as Parkinson's disease progresses, approximately 50% and 90% of patients on levodopa therapy experience debilitating dyskinesia after five and 15 years of levodopa therapy, respectively. We estimate that there are approximately 150,000 patients with LID in the United States. The only approved treatments for the treatment of LID in patients with Parkinson's disease are amantadine, Gocovri, an extended release capsule formulation of amantadine marketed by Adamas Pharmaceuticals, and Osmolex, an extended release capsule formulation of amantadine marketed by Osmotica Pharmaceuticals.

There is significant preclinical evidence in animal models that stimulating k-opioid receptors and antagonizing μ-opioid receptors represses LID. In the same preclinical model in non-human primates that showed the effect of Gocovri on LID, nalbuphine demonstrated statistically significant reduction of dyskinesia in non-human primates, maintaining anti-LID activity with chronic administration and in a dose dependent manner, and was safe and well tolerated. We believe the dual mechanism of action of nalbuphine ER could be effective in treating LID in patients with Parkinson's disease. We have written the protocol for a Phase 2 clinical trial to evaluate the effect of nalbuphine ER on LID in patients with Parkinson's disease and plan to submit an IND application in the upcoming months.

Other Chronic Pruritus Programs

Uremic Pruritus Program

Overview

Chronic kidney disease-associated pruritus, also known as uremic pruritus, can occur in patients with chronic kidney disease and is most often seen in patients receiving hemodialysis. Uremic pruritus is one of the most common conditions affecting end-stage renal disease, or ESRD, patients undergoing hemodialysis. Studies report that itchy and dry skin, symptoms of pruritus, affect 40% to 90% of ESRD patients. Yet, in clinical practice the condition is often underdiagnosed resulting in inadequate management and an underappreciated impact on patient outcomes. Data from the Dialysis Outcomes and Practice Patterns Study, or DOPPS, in 2017 demonstrated that 70% of hemodialysis patients experienced some pruritus, with 42% reporting moderate to extreme pruritus. The DOPPS started in 1996 and has tracked over 120,000 patients on hemodialysis and pertoneal dialysis and with chronic kidney disease over 20 countries.

We estimate that there are more than 650,000 patients in the United States and approximately 2 million patients worldwide who are affected by ESRD and that, among these patients, approximately 260,000 patients in the United States and 800,000 patients worldwide suffer from pruritus.

No treatment for uremic pruritus has been approved in the United States or Europe, but nalfurafine (marketed as Remitch) is approved in Japan for uremic pruritus. Treatment of uremic pruritus may include optimizing dialysis procedures as well as off-label treatments such as corticosteroids and other immunosuppressive or anti-inflammatory treatments, phototherapy and drugs such as gabapentin and Lyrica (pregabalin), prescription medicines approved for the treatment of seizures and neuropathic pain.

Clinical Development

We have conducted three clinical trials of nalbuphine ER in patients with uremic pruritus, including a Phase 2b/3 clinical trial in 373 patients with moderate to severe uremic pruritus, an open label extension of the Phase 2b/3 clinical trial and a Phase 1b clinical trial in 14 hemodialysis patients with uremic pruritus and eight healthy subjects.

Phase 2b/3 Clinical Trial

We completed a Phase 2b/3 clinical trial in June 2015 to evaluate the safety and efficacy of nalbuphine ER versus placebo in patients with uremic pruritus. The trial was a multicenter, randomized, double-blind trial conducted at 41 sites in the United States and Europe. The trial enrolled a total of 373 adult patients who had uremic pruritus, had been receiving in-center hemodialysis for at least three months, were on a schedule of three dialysis visits per week and had mean WI-NRS scores of at least 4.5 (indicating moderate to severe pruritus) over their last three dialysis visits. The patients were randomized across three treatment arms: either 108 mg or 54 mg of nalbuphine ER or placebo, each administered twice daily. The baseline mean WI-NRS scores for the three treatment arms were comparable: 6.94 for the 108 mg arm, 6.87 for the 54 mg arm and 6.75 for the placebo arm. There were three dosing periods in the trial, all of which were blinded: an initial two-week titration period during which patients received gradually increasing doses of nalbuphine ER or placebo, reaching the final assigned dose on day 15; a six-week fixed-dosing period; and a two-week off-treatment safety observation period.

The primary endpoint of the trial was the mean change in WI-NRS score at baseline to WI-NRS score over the last two weeks of the fixed-dosing period (weeks seven and eight), which we refer to as the Evaluation Period. Key secondary endpoint analyses included the following:

- change from baseline to the Evaluation Period in total Skindex-10 score, which is a questionnaire-based score assessing quality of life across 10 questions, grouped into three categories, or domains, with three questions relating to disease symptoms, three questions relating to mood and emotional distress and four questions relating to effects on social functioning; and
- change from baseline to the Evaluation Period in Itch Medical Outcomes Study, or IMOS, Sleep Scale score, which is a questionnaire-based score developed for hemodialysis patients assessing overall quality of sleep.

Efficacy Results

The following table summarizes the outcomes of the trial for the primary endpoint and key secondary endpoints. The table below also includes results from a *post hoc* analysis of change from baseline to the Evaluation Period in score for only the disease domain questions of the Skindex-10 assessment and a *post hoc* analysis of the subset of patients who entered the trial with severe itch, defined as a baseline WI-NRS score of at least 7, which we believe is notable as it shows a greater response in patients with more severe itch.

Endpoint	**Nalbuphine ER 108mg** mITT(1): n=120 Severe itch(2) : n=61	*p-value(3)*	**Nalbuphine ER 54 mg** mITT(1): n=128 Severe itch(2) : n=63	*p-value(3)*	**Placebo** mITT(1): n=123 Severe itch(2) : n=55
Primary Endpoint					
Mean change in WI-NRS score from baseline to Evaluation Period in mITT population	(3.49)	p=0.017	(3.10)	p=0.441	(2.80)
Post Hoc Analyses and Key Secondary Endpoints					
Post hoc analysis of mean change in WI-NRS scores from baseline to Evaluation Period in severe itch population	(4.48)	p=0.007	(3.44)	p=0.521	(3.16)
Change from baseline to Evaluation Period in total Skindex-10 score in mITT population	(16.99)	p=0.246	(13.82)	p=0.863	(15.01)
Post hoc analysis of change from baseline to Evaluation Period in Skindex-10 disease domain sub-score in mITT population	(6.40)	p=0.053	(5.32)	p=0.456	(5.18)
Change in IMOS Sleep Scale score from baseline to the Evaluation Period in mITT population	(15.99)	p=0.062	(13.85)	p=0.893	(12.26)
Post hoc analysis of mean change in IMOS Sleep Scale score from baseline to the Evaluation Period in severe itch population	(21.59)	p=0.006	(15.02)	p=0.506	(11.40)

(1) Represents the modified intention to treat population, which consists of all of the patients who were randomized and commenced dosing.
(2) Patients with a baseline WI-NRS score of at least 7.
(3) All p-values compare treatment group to placebo. Only the primary endpoint was powered for statistical significance.

Safety Results

The overall profile of the safety observations in the trial reflected the high rates of concomitant disease in the patient population, which is common for patients suffering from chronic renal failure. At baseline, the patient population had the following rates of serious concomitant diseases: hypertension, 98%; dyslipidemia/hyperlipidemia, 58%; diabetes, 52%; congestive heart failure, 29%; peripheral neuropathy, 28%; history of supraventricular tachycardia, 16%; history of peripheral vascular disease, 14%; history of prior myocardial infarction, 12%; and history of prior stroke, 10%.

In this trial, SAEs were frequent but were primarily related to the serious concomitant diseases associated with patients on hemodialysis or to procedural complications related to hemodialysis. During the trial, one patient on placebo died from sepsis; no other deaths occurred. Overall, 43 patients experienced at least one SAE during the eight weeks of trial dosing. Of the SAEs reported, a case of grade 3 vertigo was the only SAE considered related to study drug. The most common SAEs that were considered unrelated to study drug included congestive cardiac failure, non-cardiac chest pain, fluid overload, chronic obstructive pulmonary disease, gastrointestinal hemorrhage and hypotension. TEAEs occurred in 73%, 75% and 61% of the patients in the 108 mg, 54 mg and placebo arms, respectively. The higher rates of TEAEs in the nalbuphine ER arms as compared to placebo appeared to be primarily attributable to higher rates of TEAEs in the nalbuphine ER arms during the initial two-week titration period. During the titration period, 55% of nalbuphine ER-treated patients experienced TEAEs, as compared to 28% of patients receiving placebo. During the eight-week fixed-dosing period, 37% of nalbuphine ER-treated patients experienced TEAEs, as compared to 42% of patients receiving placebo.

The following table summarizes the most common TEAEs experienced by patients in each of the two weeks of the titration period, as well as in the fixed-dosing period, indicating the percentage of the mITT population of each arm that reported each such TEAE.

	First Week of Titration Period			Second Week of Titration Period			Fixed-Dosing Period		
TEAE	108 mg (n=120)	54 mg (n=128)	Placebo (n=123)	108 mg (n=120)	54 mg (n=128)	Placebo (n=123)	108 mg (n=120)	54 mg (n=128)	Placebo (n=123)
Nausea	18%	18%	4%	3%	3%	2%	9%	6%	3%
Vomiting	12%	17%	2%	3%	3%	2%	7%	6%	5%
Somnolence	12%	8%	2%	2%	2%	1%	1%	2%	—
Dizziness	7%	5%	—	3%	1%	—	2%	1%	—

While we believe that this trial established proof of concept for nalbuphine ER in the treatment of pruritus, we are not actively developing nalbuphine ER for uremic pruritus at this time based on our evaluation of the market dynamics, but may consider resuming development in the future.

Open Label Extension Study

We completed a six-month (24-week) open label extension study of our Phase 2b/3 clinical trial in patients with uremic pruritus in November 2015. Patients who completed the Phase 2b/3 clinical trial were able to enroll in the extension study following a safety washout period. Patients who enrolled in the extension study who had WI-NRS scores of greater than 2 were immediately admitted to the active treatment period of the study. Patients with WI-NRS scores of 2 or less entered an observation period for up to 12 weeks. Patients in this observation period began to receive active treatment only following their first WI-NRS score that was greater than 2; if they reached the end of the 12-week observation period and their WI-NRS scores remained at or below 2, they were required to leave the study.

Patients in the active treatment period received nalbuphine ER with an initial titration over three weeks according to the evolution of their itch response, at doses ranging from 27 mg, once daily, up to a maximum dose of 108 mg, twice daily, followed by up to 21 additional weeks of treatment. The variable-length observation period resulted in an active treatment period that could range from 12 to 24 weeks (including the initial titration period), depending on when the patient moved from the observation period to the active treatment period. After the initial titration period, patients were permitted one down-titration, and if their itch increased with the reduced dose, they could then return to their initial fixed dose in the study. The open label extension study enrolled 184 patients. Of these, 167 were admitted to the active treatment cohort and 51 of these patients had WI-NRS scores of at least 7, indicative of severe itch, a group we refer to as the severe itch population. Of the patients admitted to the active treatment cohort, 101 completed the open label extension study, including 31 of the patients in the severe itch population.

The patients admitted to the active treatment cohort had a mean baseline WI-NRS score of 5.59 (recorded in 166 of the 167 patients admitted) and the mean WI-NRS score at week 24 of the patients who completed the study was 2.78, amounting to a reduction of 2.70. The severe itch population had a mean baseline WI-NRS score of 8.27 and the mean WI-NRS score at week 24 of the patients in the severe itch population who completed the study was 3.48, amounting to a reduction of 4.73.

The patients admitted to the active treatment cohort had a mean baseline total Skindex-10 score of 27.63 (recorded in 166 of the 167 patients admitted) and the mean total Skindex-10 score at week 24 of the patients who completed the study was 16.61, amounting to a reduction of 10.56. The severe itch population had a mean baseline total Skindex-10 score of 40.29 and the mean total Skindex-10 score at week 24 of the patients in the severe itch population who completed the study was 18.58, amounting to a reduction of 19.97.

The patients admitted to the active treatment cohort had a mean baseline IMOS Sleep Scale score of 48.50 (recorded in 165 of the 167 patients admitted) and the mean IMOS Sleep Scale score at week 24 of the patients who completed the study was 38.54, amounting to a reduction of 8.75. The severe itch population had a mean Sleep Scale score at week 24 of the patients in the severe itch population who completed the study was 43.47, amounting to a reduction of 18.42.

We also assessed changes from baseline to week 24 in mean score for the depression-related questions of the Hospital Anxiety and Depression Scale, or HADS, which is a questionnaire-based 4-category numeric assessment scale ranging from 0 to 3 over 14 questions, with seven questions relating to anxiety and seven questions relating to depression. The patients admitted to the active treatment cohort had a mean baseline HADS depression subscale score of 6.03 (recorded in 165 of the 167 patients admitted) and the mean HADS depression subscale score at week 24 of the patients who completed the study was 4.78, amounting to a reduction of 1.15. The severe itch population had a mean baseline HADS depression subscale score of 6.80 and the mean HADS depression subscale score at week 24 of the patients in the severe itch population who completed the study was 4.77, amounting to a reduction of 1.71.

Safety observations in the extension study reflected the underlying severity of illness in the patients in the study, all of whom were on hemodialysis. Four deaths occurred during the study among the 184 enrolled patients. The primary causes of death in these four patients were: cardiac arrest, sudden death, myocardial infarction and hypertensive emergency and massive cerebral hemorrhage in the basal ganglia. The overall mortality rate, and incidence of cardiac deaths specifically, observed in the trial was consistent with the normal rates for this patient population. Among the 54 patients who reported one or more SAEs, three patients reported SAEs that were considered possibly related to study drug: one case of grade 2 gastritis that occurred in association with systemic inflammatory response syndrome; one case of grade 2 constipation that occurred in the setting of associated fluid overload; and one case of grade 2 headache that occurred in the setting of grade 2 hypotension. None of these patients died. Of the adverse effects that are commonly associated with the opiate drug class use (vertigo, constipation, nausea, vomiting, dizziness, somnolence and sedation), only nausea (occurring in 25.7% of patients) and vomiting (occurring in 19.8% of patients), occurred in greater than 10% of patients.

Other Ongoing Development Work

We plan to conduct a human abuse liability study to further characterize the abuse potential of nalbuphine. We also anticipate conducting additional standard pharmacokinetics studies required for any NDA submission including studies in specific populations, cardiovascular safety, food effect and dose proportionality studies, and other studies as needed to support marketing applications for regulatory approval in the United States and Europe.

Competition

The biopharmaceutical industry is intensely competitive and is subject to rapid and significant change. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies. If we are able to successfully develop and commercialize nalbuphine ER, it would compete with existing therapies and new therapies that may become available in the future.

Chronic Pruritus

We are developing nalbuphine ER for the treatment of pruritus associated with prurigo nodularis. Currently, there are no products approved in the United States or Europe for the treatment of pruritus associated with prurigo nodularis, however there are many products that are used to help manage pruritus associated with prurigo nodularis with which we expect that nalbuphine ER would compete if it is approved in this indication. The most common of these agents are anti-itch creams and emollients as well as oral or injectable antihistamines. All of these products have limited degrees of efficacy and are available generically. Additionally, patients may try several other agents such as 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, generally with limited success. If approved for the treatment of pruritus associated with prurigo nodularis, we expect that nalbuphine ER might also compete with product candidates currently in clinical development in this indication, including serlopitant, an oral neurokinin-1 receptor antagonist being developed by Menlo Therapeutics that is in Phase 3 clinical trials; 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 or another pruritic condition, 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 approved for the treatment of pruritus associated with PBC, nalbuphine ER may also compete with 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. Nalbuphine ER may also complete with 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 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.

Chronic Cough in Idiopathic Pulmonary Fibrosis

If nalbuphine ER is approved for the treatment of chronic cough associated with IPF, we expect that it would compete with 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.

Levodopa-Induced Dyskinesia in Parkinson's Disease

If nalbuphine ER is approved for the treatment of LID in patients with Parkinson's disease, we expect that it would compete with amantadine as well as 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 Lundbeck, 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 competitors and potential competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and commercializing products than we do. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and enrolling patients for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We expect that nalbuphine ER, if approved for marketing, will compete on the basis of, among other things, efficacy, safety, health-economic benefit, convenience of administration and delivery, price, the level of generic competition and the availability of adequate reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than nalbuphine ER. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for nalbuphine ER, which could result in our competitors establishing a strong market position before we are able to enter the market.

License Agreements

Exclusive License Agreement with Endo Pharmaceuticals

In May 2011, we entered into an agreement with Penwest (subsequently merged into its parent, Endo Pharmaceuticals Inc., or Endo) for an exclusive, worldwide, sublicenseable 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, we paid Penwest a non-creditable, non-refundable upfront license fee of $25,000. We may also become obligated to make milestone payments to Endo of $250,000, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate, such as our PRISM trial, and $750,000, 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 us, our affiliates and sublicensees. In addition, we are obligated to pay Endo a low-to-mid double-digit percentage of certain income we receive from sublicensees, based on the date of the definitive agreement under which the sublicense was granted.

Our 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, we are thereafter obligated to pay a low single-digit know-how and trademark royalty.

Under the agreement, we have granted Endo a non-exclusive, royalty-free (except for pass-through payments to third parties), sublicenseable license under our relevant patent rights, to use any improvement we make to Endo’s controlled release technology, for any product other than the products under which we are licensed by Endo.

Both we 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 we undergo specified bankruptcy, insolvency or liquidation events, and we have the right to terminate the agreement for our convenience at any time on 180 days’ notice to Endo. Additionally, if we or any of our 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 will be revoked.

Upon termination of the agreement, we 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 our corporate trademarks, then being used in connection with the licensed products. If the agreement is terminated under certain specified circumstances, we 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 we made to the licensed know-how, and any related patent rights we have, to manufacture and commercialize the licensed products.

Exclusive License Agreement with Rutgers

In November 2018, we entered into an agreement with Rutgers, The State University of New Jersey, or 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.

Under the license agreement, we paid Rutgers a minimal upfront license issue fee and agreed to pay Rutgers a minimal annual license fee. We may become obligated to make milestone payments to Rutgers in the aggregate of up to $330,500 based on the achievement of certain clinical, regulatory and sales milestones. We have also agreed to pay Rutgers a low single-digit percentage of certain income we receive from sublicensees and to pay tiered low single-digit royalties based on net sales of licensed products by us, our affiliates and sublicensees.

Our 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 us 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.

Under the agreement, Rutgers retains the right to practice under the patent rights for its own non-commercial educational and research purposes, including the right to provide the patent rights to governmental laboratories and to perform research for non-commercial purposes (provided such research is not sponsored by any for-profit entity), and to publish the research results.

Both we and Rutgers have the right to terminate the agreement upon a specified period of written notice if the other party breaches the agreement and fails to cure the breach within such specified cure period. Rutgers also has the right to terminate the agreement in the event we undergo specified bankruptcy, insolvency or liquidation events, and we have the right to terminate the agreement for our convenience at any time on 90 days' written notice to Rutgers.

We have diligence and reporting obligations under the agreement that require us to use commercially reasonable efforts to commercialize at least one licensed product in one major market country. In addition, if we do not meet certain clinical milestones within the specified time frames, we may extend the diligence period by making a payment of a low five-digit dollar amount to Rutgers. Thereafter, if we do not fulfill such clinical milestones within the specified time frames, Rutgers may terminate the agreement.

Manufacturing

We currently contract with third parties for the supply of nalbuphine hydrochloride drug substance and the manufacture of nalbuphine ER tablets for clinical trials and intend to do so for clinical and commercial supply in the future. We do not own or operate facilities for the production of clinical or commercial quantities of drug substance or drug product. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. Although we rely on contract manufacturers, we have personnel with experience to oversee our relationships with contract manufacturers.

Nalbuphine ER is manufactured from readily available starting materials using established, scalable processes that do not require any special equipment or technology. Nalbuphine hydrochloride drug substance is commercially available and manufactured at production scale. Nalbuphine ER tablets are currently manufactured at a scale sufficient for use in clinical trials. Process development work is also being planned.

We believe that our current suppliers and manufacturers have the capacity to support commercial scale production of nalbuphine ER, however we have no formal agreements with them to cover commercial production and we may seek to pursue supply or manufacturing arrangements with additional or alternative parties in the future. While we believe there are alternate sources of supply that can satisfy our clinical requirements and any future commercial requirements, replacing or adding a supplier or manufacturer could result in additional cost or delay.

Commercial Operations

In light of our stage of development, we have not yet established a marketing and sales organization. We have retained worldwide development and commercial rights for nalbuphine ER. If nalbuphine ER is approved by the FDA for any of our target indications, we intend to market and commercialize nalbuphine ER in the United States by developing our own focused, specialty sales organization targeting the physicians specializing in such conditions. In the case of prurigo nodularis, we expect that we would target a small subset of the dermatologists in the United States. For pruritus associated with PBC, we expect that we would seek to market directly to hepatologists and high-volume gastroenterologists in the United States. For chronic cough related to IPF, we expect that we would target the pulmonologists who specialize in IPF from among the 12,000 pulmonologists practicing in the United States. For LID in patients with Parkinson's disease, we expect that we would target the movement disorders specialists and high-volume neurologists in the United States. For markets outside of the United States, we expect to utilize a variety of types of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize nalbuphine ER.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for nalbuphine ER and our manufacturing and process discoveries and other know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

As of December 31, 2019, we owned four U.S. patents, two foreign patents and multiple pending U.S. and foreign patent applications that include claims relating to methods of use of nalbuphine ER. The issued patents expire between 2032 and 2033 and the patent applications, if issued as patents, would expire between 2032 and 2039.

In addition, we are party to an exclusive license agreement with Endo under we have licensed patent rights and know-how to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including nalbuphine ER. As of December 31, 2019, the intellectual property in-licensed under this agreement included five U.S. patents, three foreign patents, which include granted European patent rights that have been validated in various E.U. member states, one pending U.S. patent application (which has been allowed by the United States Patent and Trademark Office, or USPTO) and one pending foreign patent application. The licensed patents from Endo include claims relating to the formulation of nalbuphine ER. These patents expire between 2026 and 2029 and these patent applications, if issued as patents, would expire in 2026.

In addition, under our exclusive license agreement with Rutgers, we have in-licensed two issued U.S. patents and one issued Japanese patent, and additional pending applications in the United States, Europe and Canada. These patents relate to the use of nalbuphine in various movement disorders, including LID. The U.S. patents expire in 2032 and the patent applications, if granted, will expire in 2032. The Japanese patent expires in 2032.

We do not own or exclusively license any composition of matter patents for nalbuphine ER.

The terms of individual patents depend upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, the patent term is generally 20 years from the earliest claimed filing date of a nonprovisional patent application in the applicable country. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date.

Similar provisions are available in the European Union and certain other non-U.S. jurisdictions to extend the term of a patent that covers an approved drug. The expiration dates referred to above are without regard to potential patent term extension or other market exclusivity that may be available to us. However, we cannot provide any assurances that any such patent term extension of a non-U.S. patent will be obtained and, if obtained, the duration of such extension. We also protect our proprietary technology and processes, in part, by confidentiality and invention assignment agreements with our employees, consultants, scientific advisors and other contractors. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants, scientific advisors or other contractors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Our commercial success will also depend in part on not infringing the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, alter our processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize nalbuphine ER or any future product candidate may have a material adverse impact on us. If third parties prepare and file patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference or derivation proceedings in the USPTO to determine priority of invention.

Government Regulation and Product Approvals

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

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug, and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or the post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines and civil or criminal investigations and penalties brought by the FDA, the Department of Justice or other government entities, including state agencies.

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

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- completion of the manufacture, under current Good Manufacturing Practices, or cGMP, conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing;

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

Preclinical Studies

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

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of preclinical testing, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other information, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a partial clinical hold might state that a specific protocol or part of a protocol may not proceed, while other parts of a protocol or other protocols may do so. No more than 30 days after the imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following the issuance of a clinical hold or partial clinical hold, a clinical investigation may only resume once the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed or recommence.

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

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

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

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

Expanded Access to an Investigational Drug for Treatment Use

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

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

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act , or Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

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

Human Clinical Trials in Support of an NDA

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

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

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

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

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

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

Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Review and Approval of an NDA

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

The NDA is a vehicle through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2020 is $2,942,965 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2020 is $325,424. Certain exceptions and waivers are available for some of these fees, such as a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the requested additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within 10 months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of products that are not NMEs, the 10-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

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

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

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

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

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

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

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

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from 10 months to six months.

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

Accelerated Approval Pathway

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

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

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

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

The FDA's Decision on an NDA

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

If the FDA approves a new product, it may limit the approved indications for use of the product. The agency may also require testing and surveillance programs to monitor the product after the initiation of commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, such as REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

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

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

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

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

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

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

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

Section 505(b)(2) NDAs

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

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

Abbreviated New Drug Applications for Generic Drugs

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

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

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

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

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

Hatch-Waxman Act Patent Certification and the 30-Month Stay

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

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

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

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

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

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

Pediatric Studies and Exclusivity

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

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

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act.

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

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

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half of the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Health Care Law and Regulation

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

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

- the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to health care items or services that are reimbursed by non-government third-party payors, including private insurers.

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

Pharmaceutical Insurance Coverage and Health Care Reform

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

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

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

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

In March 2010, the United States Congress enacted the ACA, which, among other things, included changes to the coverage and payment for drug products under government health care programs. The ACA effected the following changes of importance to our potential product candidates:

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

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

Since enactment of the ACA, there have been, 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.

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 the Centers for Medicare & Medicaid Services 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 January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The current presidential administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, the President signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a second Executive Order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the current presidential administration announced that it will discontinue the payment of cost-sharing reduction, or CSR, payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain. In addition, the Centers for Medicare & Medicaid Services has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

Further, 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's budget proposal for fiscal year 2020 contains further drug price control measures that could be enacted during the 2020 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the current presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. 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.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of an MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

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

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014, or the Clinical Trials Regulation, was adopted. The Clinical Trials Regulation was published on June 16, 2014 but has not become effective. The Clinical Trials Regulation will be directly applicable in all the E.U. Member States, repealing the current Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

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

As of January 1, 2020, the website of the European Commission reported that the implementation of the new Clinical Trials Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit, and that the new legislation would come into effect six months after the European Commission publishes a notice of this confirmation. The website indicated that the audit was expected to commence in December 2020.

PRIME Designation in the European Union

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

Marketing Authorization

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

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

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

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

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

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

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

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

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

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the E.U. market until the expiration of the market exclusivity. The overall 10-year period will be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an NCE so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent Term Extensions in the European Union and Other Jurisdictions

The European Union also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. These periods can be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

Periods of Authorization and Renewals

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

Pediatric Studies and Exclusivity

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

Regulatory Requirements after a Marketing Authorization has been Obtained

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

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

Brexit and the Regulatory Framework in the United Kingdom

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

General Data Protection Regulation

The collection, use, disclosure, transfer or other processing of personal data of individuals in the European Union, including personal health data, is governed by the General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing notice to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business.

Pricing Decisions for Approved Products

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for the E.U. Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E.U. Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other E.U. Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly with respect to prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various E.U. Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced E.U. Member States, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Employees

As of December 31, 2019, we had 17 employees, with ten employees engaged in research and development and the remaining seven engaged in general management and administration, including finance and facilities. None of our employees are represented by labor unions or covered by collective bargaining agreements. We believe that we maintain good relations with our employees.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on March 17, 2011 under the name Trevi Therapeutics, Inc. Our principal executive offices are located at 195 Church Street, 14th Floor, New Haven, Connecticut 06510, and our telephone number is (203) 304-2499. Our website address is www.trevitherapeutics.com. The information contained on, or that can be accessed through, our website is not a part of this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference.

Item 1A. Risk Factors.

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

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since 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 $26.1 million, $20.5 million and $12.9 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $114.2 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 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.

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 years ended December 31, 2019, 2018 and 2017, we used net cash of $23.1 million, $18.3 million and $8.0 million, respectively, in our operating activities, substantially all of which related to development activities for nalbuphine ER. As of December 31, 2019, our cash and cash equivalents were $57.3 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, 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 third 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 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 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 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.

Under the protocol for our ongoing Phase 2b/3 PRISM trial, once 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 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 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 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. 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.

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

Significant outbreaks of contagious diseases, and other adverse public health developments, could have a material impact on our business operations and operating results. For example, the spread of COVID-19 has affected segments of the global economy and could affect our operations, including the potential interruption of our clinical trial activities and our supply chain. The recent outbreak of COVID-19 originated in Wuhan, China, in December 2019 and has since spread to multiple countries in Europe in which we have active clinical trial sites, which has resulted in one of those sites postponing enrollment of new patients and another site requiring remote monitoring of patients, and other sites could take similar actions. The continued spread of COVID-19 globally could also adversely affect our clinical trial operations in the United States and elsewhere, including our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 if an outbreak occurs in their geography. Further, the COVID-19 outbreak could result in delays in our clinical trials due to prioritization of hospital 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.

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 may take 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 any potential business shutdowns or disruptions. If we or any of the third parties with whom we engage, however, were to experience shutdowns or other business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively affected, which could have a material adverse impact on our business and our results of operation and financial condition.

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 serlopitant, an oral neurokinin-1 receptor antagonist being developed by Menlo Therapeutics that is in Phase 3 clinical trials; 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 Lundbeck, 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. 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, 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 Annual Report on Form 10-K 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 January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. 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.

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.

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 December 31, 2019 we had 17 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; 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.

A significant portion of our outstanding shares of common stock are eligible to be sold in the public market in the near future, which could cause the trading price of our common stock to decline significantly.

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 73.0% of our common stock as of March 16, 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. Under the Tax Act, federal net operating losses generated after December 31, 2017 are not subject to expiration, but the deductibility of such federal net operating losses is limited to 80% of our taxable income in any future taxable year. In addition, due to our Series A convertible preferred stock financing in December 2012 and the shares issued in connection with our IPO in May 2019, we were subject to an “ownership change” under Section 382 of the Internal Revenue Code of 1986, as amended. 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 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 occurred, 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 the 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 has occurred and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

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 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

Our headquarters is currently located in New Haven, Connecticut, and consists of approximately 5,600 square feet of leased office space under a lease that expires in February 2023 under which we have an option to extend the lease by an additional year. We believe that our existing facilities are adequate for our current needs; however, we may require additional space and facilities as our business expands.

Item 3. Legal Proceedings.

We are not subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock is listed on the Nasdaq Stock Market LLC under the symbol "TRVI." Trading of our common stock commenced on May 7, 2019 in connection with our initial public offering, or IPO. Prior to that time, there was no established public trading market for our common stock.

Stockholders

As of March 10, 2020, there were approximately 27 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees.

Dividend Policy

We have never declared or paid cash dividends on our common stock and we do not intend to pay any cash dividends in the foreseeable future. We currently intend to retain all available funds and any future earnings to finance the operation, development and growth of our business. In addition, the terms of any future debt or other financing that we may obtain may also preclude us from declaring or paying dividends on our common stock. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Securities Authorized for Issuance Under Equity Compensation Plan

The information concerning our equity compensation plan is incorporated by reference from the information in our Proxy Statement for our 2020 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Use of Proceeds from Registered Securities

On May 9, 2019, we closed our 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 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 December 31, 2019, 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. Selected Financial Data.

Not applicable**.**

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

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the statements contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, 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," "continue" "could," "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 Annual Report on Form 10-K, particularly including those risks identified in Part I-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 Annual Report on Form 10-K. Statements made herein are as of the date of the filing of this Annual Report on Form 10-K 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 Annual Report on Form 10-K, 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. To date, we have enrolled approximately 45% of the target number of patients. The pace of enrollment has been slower than anticipated primarily due to competition from other clinical trials and slower than planned site start-ups in Europe. We expect to report top-line data from the 14-week blinded treatment period of the PRISM trial in the second half of 2020. Additionally, the protocol for the PRISM trial provides for a sample size re-estimation analysis once 50% of the patients in the trial are evaluable for the primary endpoint. We expect to reach 50% patient enrollment during the second quarter of 2020. Once all of these patients complete the primary efficacy endpoint, the sample size re-estimation analysis will occur. We expect this analysis will occur in mid-2020. If we increase the target number of patients in the trial as a result of the re-estimation analysis, the timing of our report of top-line data may be delayed.

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. We expect to report 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 December 31, 2019, we had an accumulated deficit of $114.2 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 December 31, 2019, we had cash and cash equivalents of $57.3 million. We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into the third 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. 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 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

Interest Expense on our Term Loan Facility

In December 2014, we entered into a loan and security agreement with Solar Capital, Ltd. and Square 1 Bank under which we borrowed $15.0 million under a term loan, or the Term Loan. The Term Loan accrued interest at a floating rate equal to the one-month LIBOR plus 7.75% per annum. The Term Loan required interest-only payments until March 2016, which was extended to November 2016. After November 2016, payments on the Term Loan were made monthly in 20 equal installments of principal plus interest. In June 2018, we paid all amounts owed under the Term Loan.

Change in Fair Value of Series C Redeemable Convertible Preferred Stock Liability

The stock purchase agreement under which we sold shares of Series C preferred stock provided for the issuance and sale of our Series C preferred stock in three separate tranches. The tranches represented a free-standing financial instrument under Accounting Standards Codification, or ASC, 480 and required fair value accounting until they were settled. We recognized a liability on our consolidated balance sheet for the obligations under this financial instrument. We adjusted this liability to fair value at each reporting date and recognized the changes in fair value in our statements of operations as a component of other income (expense), net. We continued to recognize changes in the fair value of this liability through the closing of the third tranche, which occurred on January 18, 2019.

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 classified this contingent obligation for the Success Fee as a liability on our consolidated balance sheet and we adjusted this liability to fair value at each reporting date. 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 Years Ended December 31, 2019 and 2018

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

	Year Ended December 31,		
	2019	2018	Change
Operating expenses:			
Research and development	$ 19,339	$ 14,072	$ 5,267
General and administrative	7,306	4,336	2,970
Total operating expenses	26,645	18,408	8,237
Loss from operations	(26,645)	(18,408)	(8,237)
Other income (expense):			
Change in fair value of Series C redeemable convertible preferred stock liability	—	(2,105)	2,105
Change in fair value of obligation for loan success fee	(215)	(138)	(77)
Interest income	792	156	636
Interest expense	—	(174)	174
Total other income (expense), net	577	(2,261)	2,838
Loss before income tax benefit	(26,068)	(20,669)	(5,399)
Income tax benefit	18	124	(106)
Net loss	$ (26,050)	$ (20,545)	$ (5,505)

Operating Expenses

Research and Development Expenses

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

	Year Ended December 31,	
	2019	2018
Clinical development expenses	$ 15,579	$ 10,828
Personnel and related expenses	2,265	1,958
Consulting expenses and professional fees	1,077	817
Stock-based compensation expenses	143	159
Other research and development expenses	275	310
Total research and development expenses	$ 19,339	$ 14,072

Research and development expenses increased $5.3 million, or 37.4%, from $14.1 million for the year ended December 31, 2018 to $19.3 million for the year ended December 31, 2019. The increase was primarily due to a $4.8 million increase in clinical development expenses primarily related to increased activities in several clinical trials including our Phase 2b/3 PRISM trial, our Phase 2 trial in chronic cough in patients with IPF and our Phase 1b trial in patients with chronic liver disease. In addition, personnel and related expenses increased by $0.3 million as a result of an increase in our employee headcount, and consulting expenses and professional fees increased by $0.3 million as a result of our increased clinical trial activity. For the years ended December 31, 2019 and 2018, all of our research and development expenses relate to our development activity for nalbuphine ER.

General and Administrative Expenses

General and administrative expenses increased $3.0 million, or 68.5%, from $4.3 million for the year ended December 31, 2018 to $7.3 million for the year ended December 31, 2019. The increase was primarily due to an increase in personnel and stock-based compensation expenses of $1.4 million, which we incurred from the issuance of new stock option grants upon the IPO and from expanded operations, an increase in expenses related to being a public company of $1.1 million and an increase in consulting expenses and professional fees of $0.5 million.

Other Income (Expense), Net

Other income (expense), net for the year ended December 31, 2019 increased to other income, net of $0.6 million from other (expense), net of $2.3 million for the year ended December 31, 2018. The increase primarily reflects the change in fair value of our liability during the year ended December 31, 2018 for the shares of Series C preferred stock purchasable in the second and third tranches of our Series C preferred stock financing as well as increased interest income of $0.8 million 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 the Term Loan. 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. As of June 30, 2018, all amounts owed under the Term Loan 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 December 31, 2019, we had cash and cash equivalents of $57.3 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):

	Year Ended December 31,	
	2019	2018
Net cash used in operating activities	$ (23,093)	$ (18,289)
Net cash used in investing activities	(9)	(158)
Net cash provided by financing activities	73,213	3,629
Net cash increase (decrease)	$ 50,111	$ (14,818)

Operating Activities

During the year ended December 31, 2019, operating activities used $23.1 million of cash, resulting from our net loss of $26.1 million, partially offset by changes in our operating assets and liabilities of $1.6 million and non-cash charges of $1.4 million. Changes in our operating assets and liabilities for the year ended December 31, 2019 consisted primarily of a $1.4 million increase in accrued expenses, a $0.8 million increase in accounts payable, a $0.4 million increase in receivables, and a $0.2 million increase in prepaid expenses. 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 increase in receivables was primarily due to prepayments made to one of our vendors, which we expect will be paid back to us in the first half of 2020. The increase in prepaid expenses was primarily due to prepayments of our insurance policies. The non-cash charges for the year ended December 31, 2019 consisted primarily of stock-based compensation expense of $1.1 million and changes in fair value of the Success Fee of $0.2 million.

During the year ended December 31, 2018, operating activities used $18.3 million of cash, resulting from our net loss of $20.5 million and net cash used in changes in our operating assets and liabilities of $0.6 million, partially offset by non-cash charges of $2.8 million. Net cash used in changes in our operating assets and liabilities for the year ended December 31, 2018 consisted primarily of a $1.3 million increase in prepaid expenses. The increase in prepaid expenses was primarily due to increases in prepayments under our ongoing research, development and clinical trial work performed by CROs. The non-cash charges for the year ended December 31, 2018 consisted primarily of a $2.1 million expense related to the change in fair value of our Series C redeemable convertible preferred stock liability and stock-based compensation expense of $0.5 million.

Investing Activities

During the years ended December 31, 2019 and 2018, we used an insignificant amount of cash in investing activities, consisting of purchases of property and equipment.

Financing Activities

During the year ended December 31, 2019, net cash provided by financing activities was $73.2 million, primarily consisting of cash proceeds, net of underwriting discounts and commissions and placement agent fees, of $65.1 million from our IPO and concurrent private placement, and $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 costs relating to our IPO of $1.2 million and payment of the $0.7 million Success Fee.

During the year ended December 31, 2018, net cash provided by financing activities was $3.6 million, primarily consisting of net cash proceeds of $10.5 million from our sales of shares of Series C preferred stock in the second tranche of our Series C preferred stock financing in August 2018, partially offset by payments of $4.8 million on the Term Loan and $0.5 million of final fees on the Term Loan.

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. 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 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 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 third 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.

While our significant accounting policies are described in the Notes to our financial statements, we believe that the following critical accounting policies are most important to understanding and evaluating our reported financial results.

Research and Development Expenses

Research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized and recognized as an expense as the goods are delivered or the related services are performed.

We have entered into agreements with CROs, contract manufacturing organizations and other companies. Our research and development accruals are estimated based on the level of services performed, progress of the studies, including the phase or completion of events, and contracted costs. The estimated costs of research and development provided, but not yet invoiced, are included in accrued expenses on our consolidated balance sheet. If the actual timing of the performance of services or the level of effort varies from the original estimates, we will adjust the accrual accordingly. Payments made to CROs, contract manufacturing organizations and other companies under these arrangements in advance of the performance of the related services are recorded as prepaid expenses.

Stock-Based Compensation Expense

We account for stock-based compensation arrangements with employees in accordance with ASC 718, *Stock Compensation*, or ASC 718. ASC 718 requires the recognition of compensation expense, using a fair value based method, for costs related to all stock-based payments, including stock options. Our determination of the fair value of stock options on the date of grant utilizes the Black-Scholes option pricing model for stock options with time-based vesting, and is impacted by our common stock price as well as changes in assumptions regarding a number of complex and subjective variables. These variables include expected term that options will remain outstanding, expected common stock price volatility over the term of the option awards, risk-free interest rates and expected dividends.

We have awarded stock options to non-employees for consultancy services. We have adopted new guidance, effective as of January 1, 2018, which requires that non-employee share-based payment transactions be measured at the grant-date fair value and no longer remeasured at the then-current fair values at each reporting date until the stock options have vested.

The fair value of an option award is recognized over the period during which the optionee is required to provide services in exchange for the option award, known as the requisite service period (usually the vesting period) on a straight-line basis.

Estimating the fair value of equity-settled awards as of the grant date using valuation models, such as the Black-Scholes option pricing model, is affected by assumptions regarding a number of complex variables. Changes in the assumptions can materially affect the fair value and ultimately how much stock-based compensation expense is recognized. These inputs are subjective and generally require analysis and judgment to develop.

Expected Term—The expected term assumption represents the weighted average period that the stock-based awards are expected to be outstanding. We have elected to use the “simplified method” for estimating the expected term of the options, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option.

Expected Volatility—For all stock options granted to date, the volatility data was estimated based on a study of publicly traded industry peer companies. For purposes of identifying these peer companies, we considered the industry, stage of development, size and financial leverage of potential comparable companies.

Expected Dividend—The Black-Scholes valuation model calls for a single expected dividend yield as an input. We currently have no history or expectation of paying cash dividends on our common stock.

Risk-Free Interest Rate—The risk-free interest rate is based on the yield available on U.S. Treasury zero-coupon issues similar in duration to the expected term of the equity-settled award.

The following assumptions were used to calculate the fair value of awards granted during the periods indicated:

	Year Ended December 31,	
	2019	2018
Risk-free interest rate	2.0%	2.7%
Expected volatility	78.7%	70.2%
Expected dividend yield	—	—
Expected life of options (in years)	6.0	6.0

We will continue to use judgment in evaluating the expected volatility, expected terms and interest rates utilized for our stock-based compensation expense calculations on a prospective basis.

Stock-based compensation expense, is reflected in the statements of operations and comprehensive loss as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Research and development expense	$ 143	$ 159
General and administrative expense	984	337
	$ 1,127	$ 496

As of December 31, 2019, total unrecognized stock-based compensation was $3.9 million, which is expected to be recognized over the remaining vesting period of 3.0 years.

The intrinsic value of all outstanding stock options as of December 31, 2019 was approximately $0.9 million based on a common stock fair value of $3.75 per share, which was the closing price of our common stock on the Nasdaq Global Market on December 31, 2019.

Common Stock Valuations

Prior to our IPO in May 2019, the estimated fair value of the common stock underlying our stock options was determined at each grant date by our board of directors, with input from management. All options to purchase shares of our common stock were intended to be exercisable at a price per share not less than the per share fair value of our common stock underlying those options on the date of grant.

In the absence of a public trading market for our common stock prior to our IPO in May 2019, on each grant date, we developed an estimate of the fair value of our common stock based on the information known to us on the date of grant, upon a review of any recent events and their potential impact on the estimated fair value per share of the common stock, and in part on input from an independent third-party valuation. As is provided for in Section 409A of the Internal Revenue Code of 1986, as amended, or the Code, we generally relied on our valuations for up to twelve months unless we had experienced a material event that would have affected the estimated fair value of our common stock.

Our valuations of our common stock prior to our IPO in May 2019 were determined in accordance with the guidelines outlined in the American Institute of Certified Public Accountants Practice Aid, Valuation of Privately-Held-Company Equity Securities Issued as Compensation, or the Practice Aid. The methodology to determine the fair value of our common stock included estimating the fair value of the enterprise using a market approach, which estimates the fair value of the company by including an estimation of the value of the business based on guideline public companies under a number of different scenarios. The assumptions used to determine the estimated fair value of our common stock were based on numerous objective and subjective factors, combined with management judgment, including external market conditions affecting the pharmaceutical and biotechnology industry and trends within the industry; our stage of development; the rights, preferences and privileges of our convertible preferred stock relative to those of our common stock; the prices at which we sold shares of our convertible preferred stock; our financial condition and operating results, including our levels of available capital resources; the progress of our research and development efforts, our stage of development and business strategy; equity market conditions affecting comparable public companies; general U.S. market conditions; and the lack of marketability of our common stock.

The Practice Aid identifies various available methods for allocating enterprise value across classes and series of capital stock to determine the estimated fair value of common stock at each valuation date. In accordance with the Practice Aid, we considered the following methods:

- *Option Pricing Method, or OPM*—The OPM treats common stock and convertible preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceed the value of the liquidation preferences at the time of a liquidity event, such as a strategic sale or merger. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value rather than, as in the case of a regular call option, a comparison with a per share stock price. Thus, common stock is considered to be a call option with a claim on the enterprise at an exercise price equal to the remaining value immediately after the convertible preferred stock liquidation preference is paid. The OPM uses the Black-Scholes option-pricing model to price the call options. This model defines the securities' fair values as functions of the current fair value of a company and uses assumptions, such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities.
- *Probability Weighted Expected Return Method, or PWERM*—Under the PWERM methodology, the fair value of common stock is estimated based upon an analysis of future values for the company, assuming various outcomes. The common stock value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of stock. The future value of the common stock under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common stock.
- *Hybrid Method*—The hybrid method is a PWERM where the equity value in one of the scenarios is calculated using an OPM. In the hybrid method used by us, we considered an IPO, as the other potential future liquidity event. The equity value for the IPO scenario was determined using the guideline public company, or GPC, method under the market approach. The relative probability of the IPO scenario was determined based on an analysis of market conditions at the time and our expectations as to the timing and likely prospects of the IPO at each valuation date. In our application of the GPC method, we considered publicly traded companies in the biopharmaceutical industry that had a similar profile to ours as well as recently completed IPOs as indicators of our estimated future value in an IPO. We then discounted that future value back to the valuation date at an appropriate discount rate.

Based on our early stage of development and other relevant factors, our board of directors determined that the OPM was the most appropriate method for allocating our enterprise value to determine the estimated fair value of our common stock for the valuation performed for December 2017, which resulted in our board of directors determining that the fair value of our common stock was $3.33. Following its determination in early 2018 that we should explore a potential IPO, our board of directors determined that the Hybrid Method was the most appropriate method for allocating our enterprise value to determine the estimated fair value of our common stock for valuations performed for April 2018, September 2018 and December 2018, which resulted in the fair value of our common stock being $6.65, $9.12 and $9.31, respectively.

In determining the estimated fair value of our common stock prior to our IPO in May 2019, our board of directors also considered the fact that our stockholders could not freely trade our common stock in the public markets. Accordingly, our board of directors applied discounts to reflect the lack of marketability of our common stock based on the weighted-average expected time to liquidity. The estimated fair value of our common stock at each grant date reflected a non-marketability discount partially based on the anticipated likelihood and timing of a future liquidity event.

Subsequent to the completion of our IPO in May 2019, the fair value of our common stock has been determined based on the closing price of our common stock as reported on the date of grant on the primary stock exchange on which our common stock is traded.

Income Taxes

We provide for income taxes under the asset and liability method. Current income tax expense or benefit represents the amount of income taxes expected to be payable or refundable for the current year. Deferred income tax assets and liabilities are determined based on differences between the financial statement reporting and tax bases of assets and liabilities and net operating loss and credit carryforwards, and are measured using the enacted tax rates and laws that will be in effect when such items are expected to reverse. Deferred income tax assets are reduced, as necessary, by a valuation allowance when management determines it is more likely than not that some or all of the tax benefits will not be realized.

We account for uncertain tax positions in accordance with ASC 740, *Accounting for Uncertainty in Income Taxes*, or ASC 740. We assess all material positions taken in any income tax return, including all significant uncertain positions, in all tax years that are still subject to assessment or challenge by relevant taxing authorities. Assessing an uncertain tax position begins with the initial determination of the position's sustainability and is measured at the largest amount of benefit that is greater than fifty percent likely of being realized upon ultimate settlement. As of each balance sheet date, unresolved uncertain tax positions must be reassessed, and we will determine whether (i) the factors underlying the sustainability assertion have changed and (ii) the amount of the recognized tax benefit is still appropriate. The recognition and measurement of tax benefits requires significant judgment. Judgments concerning the recognition and measurement of a tax benefit might change as new information becomes available.

As of December 31, 2019, our total deferred tax assets were $33.3 million. Due to our lack of earnings history and uncertainties surrounding our ability to generate future taxable income, the net deferred tax assets have been fully offset by a valuation allowance. The deferred tax assets were primarily comprised of federal and state tax net operating loss, or NOL, carryforwards; which totaled approximately $106.8 million at December 31, 2019. Due to our Series A preferred stock financing in December 2012 and the shares we issued in connection with our IPO in May 2019, we were subject to an "ownership change" under Section 382 of the Code. As a result, our ability to use $91.3 million of these NOL carryforwards 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 occurred, our ability to use our NOL carryforwards might be further limited.

Fair Value Measurements

Our financial instruments have consisted of cash and cash equivalents, income tax receivable, accounts payable, accrued expenses, term loan payable, Series C redeemable convertible preferred stock liability and obligation for loan success fee. 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, income tax receivable, 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. The fair value of the obligation for loan success fee has been estimated utilizing a probability-weighted income approach, including variables for the timing of the success event and other probability estimates. The fair value of Series C redeemable convertible preferred stock liability has been estimated as the excess, if any, of the fair value of our Series C preferred stock over the purchase price of any outstanding tranches that may be sold pursuant to our stock purchase agreement referred to in "—Components of Operating Results—Other Income (Expense), Net—Change in Fair Value of Series C Redeemable Convertible Preferred Stock Liability".

Current accounting guidance defines fair value, establishes a framework for measuring fair value in accordance with 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 or 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.

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 14 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for discussion regarding our commitments and contingent commitments.

JOBS Act Accounting Election

The Jumpstart Our Business Startups Act of 2012, as amended, or JOBS Act, permits emerging growth companies such as us to take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Recently Adopted Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2016-02 titled *Leases*, or ASU 2016-02, which requires rights and obligations arising from both operating and capital leases to be reported on the Consolidated Balance Sheet, and to disclose quantitative and qualitative information about lease transactions (such as information about variable lease payments and options to renew and terminate leases). ASU 2016-02 was effective for fiscal years beginning after December 15, 2018, with early adoption permitted.

We adopted this new guidance as of January 1, 2019, which included an assessment of the impact of the new guidance on the consolidated financial statements. We utilized the transition practical expedient added by the FASB, which eliminated the requirement that entities apply the new lease standard to the comparative periods presented in the year of adoption. We elected to use the package of practical expedients that allowed us to not reassess: (1) whether any expired or existing contracts were or contained leases, (2) lease classification for any expired or existing leases and (3) initial direct costs for any expired or existing leases. We used the practical expedient that allows lessees to treat the lease and non-lease components of leases as a single lease component. The adoption of this standard resulted in the recognition of a right-of-use asset of $379 and related lease liabilities of $424 related to our operating lease commitments on the Consolidated Balance Sheet as of January 1, 2019 *(Note 4)*. The impact of adoption of the new leasing standard did not have a material impact on the Consolidated Statement of Operations during the year ended December 31, 2019.

Recently Issued Accounting Pronouncements

In December 2019, the FASB issued ASU 2019-12, *Simplifying the Accounting for Income Taxes*. The list of changes is comprehensive and many will not have a significant effect on our consolidated financial reporting. The changes include removing exceptions to incremental intraperiod tax allocation of losses and gains from different financial statement components, exceptions to the method of recognizing income taxes on interim period losses and exceptions to deferred tax liability recognition related to foreign subsidiary investments. In addition, ASU 2019-12 requires that entities recognize franchise tax based on an incremental method, requires an entity to evaluate the accounting for step-ups in the tax basis of goodwill as inside or outside of a business combination, and removes the requirement to allocate the current and deferred tax provision among entities in stand-alone financial statement reporting. ASU 2019-12 also now requires that an entity reflect enacted changes in tax laws in the annual effective rate, and other codification adjustments have been made to employee stock ownership plans. For public business entities, the amendments in ASU 2019-12 are effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020. Early adoption of ASU 2019-12 is permitted, including adoption in any interim period for public business entities for periods for which financial statements have not yet been issued. An entity that elects to early adopt the amendments in an interim period should reflect any adjustments as of the beginning of the annual period that includes that interim period. Additionally, an entity that elects early adoption must adopt all the amendments in the same period. We are currently evaluating whether to early adopt ASU 2019-12 in the first interim period of the year ending December 31, 2020.

In June 2016, the FASB issued ASU 2016-13, Financial Instruments — Credit Losses (Topic 326), Measurement of Credit Losses on Financial Instruments, which changes the way credit losses on certain financial instruments are estimated. ASU 2016-13 is effective for fiscal years beginning after December 15, 2019, with early adoption permitted. We do not expect that the adoption of ASU 2016-13 will have a material effect on our Consolidated Financial Statements.

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

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates or exchange rates. As of December 31, 2019, we had cash and cash equivalents of $57.3 million, primarily held in interest-bearing money market accounts, which would be affected by changes in the general level of United States interest rates. However, due to the short-term maturities and the low-risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our cash and cash equivalents.

We do not believe that inflation, interest rate changes or exchange rate fluctuations had a significant impact on our results of operations for any periods presented herein.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15 of Part IV of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, 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, or the Exchange Act, as of December 31, 2019. 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 December 31, 2019, 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.

Management's Report on Internal Control over Financial Reporting

This annual report does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of the company's registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

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 December 31, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item 10 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) Financial Statements

The following documents are included on pages F-1 through F-32 attached hereto and are filed as part of this Annual Report on Form 10-K.

(2) Financial Statement Schedules:

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(3) Exhibits.

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

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of Trevi Therapeutics, Inc. (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on May 9, 2019)
3.2	Amended and Restated Bylaws of Trevi Therapeutics, Inc. (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on May 9, 2019)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
4.2*	Description of Registrant's Securities
10.1	Second Amended and Restated Investors' Rights Agreement dated as of July 14, 2017 (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.2+	2012 Stock Incentive Plan, as amended (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.3+	Form of Nonstatutory Stock Option Agreement under the 2012 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.4+	2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.5+	Form of Stock Option Agreement under the 2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.6+	2019 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.7	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

10.8+	Trevi Therapeutics, Inc. Executive Separation Benefits and Retention Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on September 24, 2019)
10.9+	Employment Agreement, dated December 4, 2012, by and between the Registrant and Jennifer L. Good (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.10+*	Offer Letter, dated December 4, 2012, by and between the Registrant and Thomas R. Sciascia
10.11+	Offer Letter, dated August 29, 2018, by and between the Registrant and Yann Mazabraud (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.12+	Indefinite Term Employment Contract, dated August 29, 2018, by and between the Registrant and Yann Mazabraud (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.13+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.14	Indenture of Lease, dated February 6, 2013, by and between First Niagara Bank, N.A. and the Registrant (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.15	First Amendment to Lease, dated December 5, 2017, by and between the Registrant and 195 Church Street Associates, LLC (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.16†	Exclusive License Agreement, dated as of May 13, 2011, by and between the Registrant and Penwest Pharmaceuticals Co. (incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.17†	Exclusive License Agreement between the Registrant and Rutgers, the State University of New Jersey, effective November 6, 2018 (incorporated by reference to Exhibit 10.16 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.18	Share Purchase Agreement, dated as of May 6, 2019, by and between the Registrant and New Enterprise Associates 16, L.P. (incorporated by reference to Exhibit 10.17 to Amendment No. 3 to Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on May 7, 2019)
21.1	List of Subsidiaries (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
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.

\+ Management contract or compensatory plan or arrangement.

† Confidential treatment has been granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

None.

SIGNATURES

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

TREVI THERAPEUTICS, INC.

Date: March 16, 2020 By: /s/ Jennifer Good

Jennifer Good
President and Chief Executive Officer

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

Name	Title	Date
/s/ Jennifer Good **Jennifer Good**	President and Chief Executive Officer, Director (Principal Executive Officer)	March 16, 2020
/s/ Christopher Seiter **Christopher Seiter**	Chief Financial Officer (Principal Financial Officer)	March 16, 2020
/s/ Frank Muscolo **Frank Muscolo**	Controller (Principal Accounting Officer)	March 16, 2020
/s/ David Meeker, M.D. **David Meeker, M.D.**	Chairman of the Board	March 16, 2020
/s/ James V. Cassella, Ph.D. **James V. Cassella, Ph.D.**	Director	March 16, 2020
/s/ Michael Heffernan **Michael Heffernan**	Director	March 16, 2020
/s/ Edward Mathers **Edward Mathers**	Director	March 16, 2020
/s/ Annie Mitsak, Ph.D. **Annie Mitsak, Ph.D.**	Director	March 16, 2020
/s/ Anne VanLent **Anne VanLent**	Director	March 16, 2020

Trevi Therapeutics, Inc.

Index to Consolidated Financial Statements

Years Ended December 31, 2019 and 2018

Contents

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Trevi Therapeutics, Inc.

Opinion on the Financial Statements

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

Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2013.

Stamford, Connecticut

March 16, 2020

Trevi Therapeutics, Inc.

Consolidated Balance Sheets

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

	December 31,	
	2019	**2018**
Assets		
Current assets:		
Cash and cash equivalents	$ 57,313	$ 7,202
Tax credit and other receivables	558	184
Prepaid expenses	1,681	1,438
Total current assets	59,552	8,824
Deferred offering costs	—	1,534
Operating lease right-of-use asset	312	—
Security deposit	19	19
Property, equipment and leasehold improvements, net	118	149
Total assets	$ 60,001	$ 10,526
Liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 1,599	$ 603
Accrued expenses	3,501	2,073
Operating lease liability - current portion	99	—
Total current liabilities	5,199	2,676
Obligation for loan success fee	—	460
Series C redeemable convertible preferred stock liability	—	1,096
Operating lease liability - long term portion	257	46
Commitments and contingencies (Note 14)		
Series A redeemable convertible preferred stock: no shares and 15,387,923 shares authorized, issued and outstanding at December 31, 2019 and 2018, respectively; liquidation preference of $0 and $20,469 at December 31, 2019 and 2018, respectively.	—	21,033
Series B redeemable convertible preferred stock: no shares and 22,608,695 shares authorized, issued and outstanding at December 31, 2019 and 2018, respectively; liquidation preference of $0 and $32,900 at December 31, 2019 and 2018, respectively.	—	33,686
Series C redeemable convertible preferred stock: no shares and 48,200,412 shares authorized at December 31, 2019 and 2018, respectively; no shares and 38,097,672 shares issued and outstanding at December 31, 2019 and 2018, respectively; liquidation preference of $0 and $59,798 at December 31, 2019 and 2018, respectively.	—	61,023
Stockholders' equity (deficit):		
Common stock: $0.001 par value; 200,000,000 and 101,929,904 shares authorized at December 31, 2019 and 2018, respectively; 17,834,570 and 438,600 shares issued and outstanding at December 31, 2019 and 2018, respectively.	18	4
Preferred stock: $0.001 par value; 5,000,000 shares and no shares authorized at December 31, 2019 and 2018, respectively; no shares issued or outstanding at December 31, 2019 or 2018.	—	—
Additional paid-in capital	168,746	—
Accumulated deficit	(114,219)	(109,498)
Total stockholders' equity (deficit)	54,545	(109,494)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 60,001	$ 10,526

See accompanying notes.

Trevi Therapeutics, Inc.

Consolidated Statements of Operations

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

	For the Year Ended December 31,	
	2019	2018
Operating expenses:		
Research and development	$ 19,339	$ 14,072
General and administrative	7,306	4,336
Total operating expenses	26,645	18,408
Loss from operations	(26,645)	(18,408)
Other income (expense):		
Change in fair value of Series C redeemable convertible preferred stock liability	—	(2,105)
Change in fair value of obligation for loan success fee	(215)	(138)
Interest income	792	156
Interest expense	—	(174)
Total other income (expense), net	577	(2,261)
Loss before income tax benefit	(26,068)	(20,669)
Income tax benefit	18	124
Net loss	$ (26,050)	$ (20,545)
Accretion of redeemable convertible preferred stock	1,535	370
Dividends accrued on redeemable convertible preferred stock	(2,239)	(5,402)
Adjusted net loss attributable to common stockholders	$ (26,754)	$ (25,577)
Basic and diluted net loss per common share outstanding	$ (2.28)	$ (58.44)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	11,735,781	437,610

See accompanying notes.

Trevi Therapeutics, Inc.

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

(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, 2017	15,387,923	$ 20,479	22,608,695	$ 32,640	30,886,507	$ 46,087	432,921	$ 4	—	(84,432)	(84,428)
Stock-based compensation	—	—	—	—	—	—	—	—	496	—	496
Issuance of common stock from exercise of stock options	—	—	—	—	—	—	5,679	—	13	—	13
Issuance of Series C redeemable convertible preferred stock, net of issuance costs	—	—	—	—	7,211,165	11,506	—	—	—	—	—
Dividends accrued on redeemable convertible preferred stock	—	923	—	1,560	—	2,918	—	—	(509)	(4,892)	(5,401)
Accretion (amortization) of premium (discount) on issuance of redeemable convertible preferred stock	—	(4)	—	20	—	—	—	—	—	(16)	(16)
Accretion of discount on investor rights/obligation	—	54	—	76	—	—	—	—	—	(130)	(130)
Adjustment for excess (shortfall) of fair value over liquidation value of redeemable convertible preferred stock	—	(424)	—	(613)	—	403	—	—	—	634	634
Accretion of issuance costs on redeemable convertible preferred stock	—	5	—	3	—	109	—	—	—	(117)	(117)
Net loss	—	—	—	—	—	—	—	—	—	(20,545)	(20,545)
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	—	—	—	—	—	—	—	—	1,127	—	1,127
Issuance of common stock from exercise of stock options	—	—	—	—	—	—	14,736	—	38	—	38
Issuance of Series C redeemable convertible preferred stock, net of issuance costs	—	—	—	—	6,849,315	11,059	—	—	—	—	—
Dividends accrued on redeemable convertible preferred stock	5,406,844	326	6,478,999	551	3,792,386	1,362	—	—	—	(2,239)	(2,239)
Accretion (amortization) of premium (discount) on issuance of redeemable convertible preferred stock	—	(7)	—	31	—	—	—	—	—	(24)	(24)
Accretion of discount on investor rights/obligation	—	84	—	117	—	—	—	—		(201)	(201)
Adjustment for excess (shortfall) of fair value over liquidation value of redeemable convertible preferred stock	—	(651)	—	(940)	—	(403)	—	—	—	1,994	1,994
Accretion of issuance costs on redeemable convertible preferred stock	—	7	—	4	—	223	—	—	—	(234)	(234)
Conversion of redeemable convertible preferred stock to common stock in connection with initial public offering	(20,794,767)	(20,792)	(29,087,694)	(33,449)	(48,739,373)	(73,264)	10,381,234	7	105,464	22,033	127,504
Issuance of common stock upon completion of initial public offering, net of underwriting discounts and commissions, and issuance costs	—	—	—	—	—	—	5,500,000	5	48,169	—	48,174
Issuance of common stock upon completion of private placement, net of private placement agent fees	—	—	—	—	—	—	1,500,000	2	13,948	—	13,950
Net loss	—	—	—	—	—	—	—	—	—	(26,050)	(26,050)
Balance at December 31, 2019	—	$ —	—	$ —	—	$ —	17,834,570	$ 18	$ 168,746	$ (114,219)	$ 54,545

See accompanying notes.

Trevi Therapeutics, Inc.

Consolidated Statements of Cash Flows

(Amounts in thousands)

	For the Year Ended December 31,	
	2019	**2018**
Operating activities		
Net loss	$ (26,050)	$ (20,545)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	39	23
Changes in fair value of Series C redeemable convertible preferred stock liability	—	2,105
Changes in fair value of obligation for loan success fee	215	138
Accretion/accrual of term loan discounts and debt issuance costs	—	60
Stock-based compensation	1,127	496
Changes in operating assets and liabilities:		
Receivables	(374)	(135)
Prepaid expenses	(243)	(1,345)
Accounts payable	777	66
Accrued expenses	1,416	772
Security deposit	—	33
Deferred lease obligation	—	43
Net cash used in operating activities	(23,093)	(18,289)
Investing activities		
Acquisitions of property, equipment and leasehold improvements	(9)	(158)
Net cash used in investing activities	(9)	(158)
Financing activities		
Repayments of term loan	—	(4,813)
Payment of final fees on term loan	—	(533)
Payment of loan success fee	(675)	—
Proceeds from exercises of stock options	38	13
Proceeds from sale of Series C redeemable convertible preferred stock, net of issuance costs	9,963	10,496
Proceeds from issuance of common shares upon completion of initial public offering, net of underwriting commissions and discounts	51,150	—
Payments of initial public offering costs	(1,213)	(1,534)
Proceeds from private placement, net of private placement agent fees	13,950	—
Net cash provided by financing activities	73,213	3,629
Net cash increase (decrease) for year	50,111	(14,818)
Cash and cash equivalents at beginning of year	7,202	22,020
Cash and cash equivalents at end of year	$ 57,313	$ 7,202
Supplemental disclosure of cash flow information		
Interest paid	$ —	$ 152
Income taxes paid	$ —	$ —
State research tax credits exchanged for cash	$ 124	$ 35
Supplemental disclosure of non-cash financing activities		
Dividends accrued on redeemable convertible preferred stock	$ 2,239	$ 5,402
Series C redeemable convertible preferred stock liability reclassified to Series C Preferred Stock	$ —	$ 1,009
Accretion on redeemable convertible preferred stock	$ (1,535)	$ (370)

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 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 $26.1 million and $20.5 million for the years ended December 31, 2019 and 2018, respectively. In addition, as of December 31, 2019, the Company had an accumulated deficit of $114.2 million. The Company expects to continue to generate operating losses for the foreseeable future. As of March 16, 2020, the issuance date of these Consolidated Financial Statements, the Company expects that its cash and cash equivalents of $57.3 million as of December 31, 2019, will be sufficient to fund its operating expenses and capital expenditure requirements through at least 12 months from the date of issuance of these Consolidated Financial Statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying 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 December 31, 2019 for potential recognition or disclosure in the 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 accounting principles generally accepted in the United States of America ("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 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.

Cash Equivalents

The Company classifies short-term, highly liquid investments with an original term of three months or less at the date of purchase as cash equivalents.

Fair Value Measurements

The Company's financial instruments have consisted of cash and cash equivalents, tax credit and other receivables, accounts payable, accrued expenses, obligation for loan success fee and Series C redeemable convertible preferred stock liability *(Note 7 and Note 9).* 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. The fair value of the obligation for loan success fee was estimated utilizing a probability-weighted income approach, including variables for the timing of the success event and other probability estimates. The fair value of Series C redeemable convertible preferred stock liability at December 31, 2018 was estimated as the excess, if any, of the fair value of the Company's Series C redeemable convertible preferred stock ("Series C Preferred Stock") over the purchase price of any outstanding tranches that had not been sold pursuant to the Series C Preferred Stock purchase agreement (the "Series C Purchase Agreement") as of December 31, 2018.

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.

The following table summarizes the financial liabilities measured at fair value on a recurring basis as of December 31, 2018, and the basis for that measurement, by level within the fair value hierarchy *(Note 7 and Note 9)*. There were no such financial liabilities as of December 31, 2019:

	Balance December 31, 2018	Level 1	Level 2	Level 3
Financial liabilities				
Series C redeemable convertible preferred stock liability	$ 1,096	$ —	$ —	$ 1,096
Obligation for loan success fee	460	—	—	460
	$ 1,556	$ —	$ —	$ 1,556

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

	December 31,	
	2019	2018
Financial liabilities		
Balance at beginning of year(1)	$ 1,556	$ 322
Unrealized loss on Series C redeemable convertible preferred stock liability	—	2,105
Unrealized loss on obligation for loan success fee	215	138
Net settlements(2)	(1,771)	(1,009)
Ending balance	$ —	$ 1,556

(1) The balance at January 1, 2018 relates to the obligation for the loan success fee.

(2) The net settlements in 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. The net settlements in 2018 relate to the $1,009 fair value of the Series C redeemable convertible preferred stock liability at the time the second tranche of Series C redeemable convertible preferred stock shares was issued.

Property, Equipment and Leasehold Improvements

Property, equipment and leasehold improvements (consisting of furniture, computer and office equipment and leasehold improvements) are stated at cost, net of accumulated depreciation. Depreciation is calculated using the straight-line method over the estimated useful lives of the respective assets (three years for computer equipment, five years for furniture and office equipment and the shorter of the term of the lease or useful life for leasehold improvements).

Impairment of Long-Lived Assets

ASC 360, *Property, Plant, and Equipment*, addresses the financial accounting and reporting for impairment or disposal of long-lived assets. The Company reviews the recorded values of long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of an asset or group of assets may not be fully recoverable. There was no impairment or disposal of long-lived assets during the years ended December 31, 2019 and 2018, respectively.

Foreign Currency Transactions

The Company, at times, contracts with vendors and consultants outside of the United States, resulting in liabilities denominated in foreign currency. The transactions are recorded in U.S. dollars on the transaction dates and any currency fluctuation through the payment date is recorded as currency gains or losses in the Consolidated Statements of Operations. Net foreign currency gains and losses in 2019 and 2018 were insignificant.

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. Deferred offering costs capitalized as of December 31, 2018 were $1,534. The Company's IPO was completed in May 2019 and these costs, as well as additional IPO costs incurred in 2019, were recorded as a reduction to stockholders' equity (deficit). As a result, as of December 31, 2019, the Company did not have any deferred offering costs.

Research and Development Expenses

All of the Company's 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 ("CROs") to conduct certain research and development activities on the Company's behalf. The Company does not allocate its costs by each indication for which it is developing nalbuphine ER, as a significant amount of the Company's development activities broadly support all indications. In addition, several of the Company's departments support the Company's nalbuphine ER drug candidate development program and the Company does not identify internal costs for each potential indication. The Company expenses both internal and external research and development expenses as they are incurred.

Accrued Research and Development

The Company has entered into agreements with CROs, contract manufacturing organizations ("CMOs") and other companies. The Company's research and development accruals are estimated based on the level of services performed, progress of the studies, including the phase or completion of events, and contracted costs. The estimated costs of research and development provided, but not yet invoiced, are included in accrued expenses on the Consolidated Balance Sheet. If the actual timing of the performance of services or the level of effort varies from the original estimates, the Company will adjust the accrual accordingly. Payments made to CROs, CMOs and other companies under these arrangements in advance of the performance of the related services are recorded as prepaid expenses.

Patent Costs

All patent-related costs in connection with filing and prosecuting patent applications are expensed to general and administrative expense as incurred, as recoverability of such expenditures is uncertain.

Stock-Based Compensation

The Company accounts for stock-based compensation arrangements with employees in accordance with ASC 718, *Stock Compensation* ("ASC 718"). ASC 718 requires the recognition of compensation expense, using a fair value based method, for costs related to all stock-based payments including stock options. The Company's determination of the fair value of stock options on the date of grant utilizes the Black-Scholes option-pricing model for stock options with time-based vesting, and is impacted by the price of its common stock as well as changes in assumptions regarding a number of complex and subjective variables. These variables include expected term that options will remain outstanding, expected common stock price volatility over the term of the option awards, risk-free interest rates and expected dividends.

The fair value is recognized over the period during which an optionee is required to provide services in exchange for the option award, known as the requisite service period (usually the vesting period) on a straight-line basis.

Estimating the fair value of equity-settled awards as of the grant date using valuation models, such as the Black-Scholes option pricing model, is affected by assumptions regarding a number of complex variables. Changes in the assumptions can materially affect the fair value and ultimately how much stock-based compensation expense is recognized. These inputs are subjective and generally require analysis and judgment to develop.

Expected Term—The expected term assumption represents the weighted average period that the stock-based awards are expected to be outstanding. The Company has elected to use the "simplified method" for estimating the expected term of the options, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option.

Expected Volatility—For all stock options granted to date, the volatility data was estimated based on a study of publicly traded industry peer companies. For purposes of identifying these peer companies, the Company considered the industry, stage of development, size and financial leverage of potential comparable companies.

Expected Dividend—The Black-Scholes valuation model calls for a single expected dividend yield as an input. The Company currently has no history or expectation of paying cash dividends on its common stock.

Risk-Free Interest Rate—The risk-free interest rate is based on the yield available on U.S. Treasury zero-coupon issues similar in duration to the expected term of the equity-settled award.

Prior to the Company's IPO in May 2019, the estimated fair value of the common stock underlying the Company's stock options was determined at each grant date by the Company's board of directors, with input from management. All options to purchase shares of common stock were intended to be exercisable at a price per share not less than the per share fair value of the Company's common stock underlying those options on the date of grant.

In the absence of a public trading market for the Company's common stock prior to the Company's IPO in May 2019, on each grant date, the Company developed an estimate of the fair value of its common stock based on the information known to the Company on the date of grant, upon a review of any recent events and their potential impact on the estimated fair value per share of the common stock, and in part on input from an independent third-party valuation. As is provided for in Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), the Company generally relied on valuations for up to twelve months unless the Company had experienced a material event that would have affected the estimated fair value of its common stock.

The valuations of the Company's common stock performed prior to the Company's IPO in May 2019, were determined in accordance with the guidelines outlined in the American Institute of Certified Public Accountants Practice Aid, Valuation of Privately-Held-Company Equity Securities Issued as Compensation (the "Practice Aid"). The methodology to determine the fair value of common stock included estimating the fair value of the enterprise using a market approach, which estimates the fair value of the Company by including an estimation of the value of the business based on guideline public companies under a number of different scenarios. The assumptions used to determine the estimated fair value of the Company's common stock were based on numerous objective and subjective factors, combined with management judgment, including external market conditions affecting the pharmaceutical and biotechnology industry and trends within the industry; the Company's stage of development; the rights, preferences and privileges of the Company's convertible preferred stock relative to those of the Company's common stock; the prices at which the Company sold shares of convertible preferred stock; the Company's financial condition and operating results, including the Company's levels of available capital resources; the progress of the Company's research and development efforts, stage of development and business strategy; equity market conditions affecting comparable public companies; general U.S. market conditions; and the lack of marketability of the Company's common stock.

The Practice Aid identifies various available methods for allocating enterprise value across classes and series of capital stock to determine the estimated fair value of common stock at each valuation date. In accordance with the Practice Aid, the Company considered the following methods:

- Option Pricing Method ("OPM")—The OPM treats common stock and convertible preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceed the value of the liquidation preferences at the time of a liquidity event, such as a strategic sale or merger. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value rather than, as in the case of a regular call option, a comparison with a per share stock price. Thus, common stock is considered to be a call option with a claim on the enterprise at an exercise price equal to the remaining value immediately after the convertible preferred stock liquidation preference is paid. The OPM uses the Black-Scholes option-pricing model to price the call options. This model defines the securities' fair values as functions of the current fair value of a company and uses assumptions, such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities.

- Probability Weighted Expected Return Method ("PWERM")—Under the PWERM methodology, the fair value of common stock is estimated based upon an analysis of future values for the company, assuming various outcomes. The common stock value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of stock. The future value of the common stock under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common stock.
- Hybrid Method—The hybrid method is a PWERM where the equity value in one of the scenarios is calculated using an OPM. In the hybrid method used by the Company, it considered an IPO as the other potential future liquidity event. The equity value for the IPO scenario was determined using the guideline public company ("GPC"), method under the market approach. The relative probability of the IPO scenario was determined based on an analysis of market conditions at the time and expectations as to the timing and likely prospects of the IPO at each valuation date. In application of the GPC method, the Company considered publicly traded companies in the biopharmaceutical industry that had a similar profile to the Company's as well as recently completed IPOs as indicators of estimated future value in an IPO. The Company then discounted that future value back to the valuation date at an appropriate discount rate.

Based on the Company's early stage of development and other relevant factors, the board of directors determined that the OPM was the most appropriate method for allocating enterprise value to determine the estimated fair value of the Company's common stock for the valuation performed for December 2017, which resulted in the board of directors determining that the fair value of common stock was $3.33. Following its determination in early 2018 that the Company should explore a potential IPO, the Company's board of directors determined that the Hybrid Method was the most appropriate method for allocating the enterprise value to determine the estimated fair value of common stock for valuations performed for April 2018, September 2018 and December 2018, which resulted in the fair value of common stock being $6.65, $9.12 and $9.31, respectively.

In determining the estimated fair value of the Company's common stock prior to Company's IPO in May 2019, the board of directors also considered the fact that the Company's stockholders could not freely trade the Company's common stock in the public markets. Accordingly, the Company's board of directors applied discounts to reflect the lack of marketability of common stock based on the weighted-average expected time to liquidity. The estimated fair value of the Company's common stock at each grant date reflected a non-marketability discount partially based on the anticipated likelihood and timing of a future liquidity event.

Subsequent to the completion of the Company's IPO in May 2019, the fair value of the Company's common stock has been determined based on the closing price of the Company's common stock as reported on the date of grant on the primary stock exchange on which the Company's common stock is traded.

The Company has awarded stock options to non-employees for consultancy services. The Company has adopted Accounting Standards Update ("ASU") No. 2018-07 titled *Compensation—Stock Compensation (Topic 718): Improvements to Non-Employee Share-Based Payment Accounting*, with effect from January 1, 2018, which requires that non-employee share-based payment transactions be measured at the grant-date fair value and no longer remeasured at the then-current fair values at each reporting date until the stock options have vested.

Income Taxes

The Company accounts for income taxes using the asset and liability method. Under this method, deferred tax assets and liabilities are determined based on differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Deferred income tax assets are reduced, as necessary, by a valuation allowance when management determines it is more likely than not that some or all of the tax benefits will not be realized.

The Company applies the provisions of ASC 740, *Income Taxes* ("ASC 740"), which prescribes a comprehensive model for how a company should recognize, measure, present, and disclose in its financial statements uncertain tax positions that the company has taken or expects to take on a tax return. These Consolidated Financial Statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. It is the opinion of Company management that there are no material uncertainties regarding the tax positions that the Company has taken through December 31, 2019 and December 31, 2018. The Company does not have any interest or penalties accrued related to tax positions as it does not have any unrecognized tax benefits. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of interest expense.

Redeemable Convertible Preferred Shares

As of December 31, 2018 and prior to the Company's IPO, shares of the Company's redeemable convertible preferred stock were redeemable at the option of the holder on or after July 14, 2020 and carried a cumulative coupon dividend rate of 6%. The redemption amount was the greater of the liquidation value (invested amount plus accruing dividends) or the fair value of the shares of preferred stock on the date of redemption. The Company was accounting for its shares of preferred stock under the requirements of ASC 480, *Distinguishing Liabilities from Equity* ("ASC 480"), which establishes standards for how an issuer classifies and measures certain financial instruments with characteristics of both liabilities and equity. The carrying value of the shares of preferred stock was presented as temporary equity and was adjusted by periodic accretions so that the carrying amount would equal the redemption amount at the estimated date that the shares of preferred stock would be redeemed. These adjustments were effected through charges against additional paid-in capital, to the extent it was available, or accumulated deficit. For all preferred stock issuances, the difference between the amount invested by the holders of the shares of preferred stock, net of issuance costs and premiums (or discounts), as compared to the redemption value was recorded as accretion over the redemption period of the shares of preferred stock. The accretion was added to net loss to arrive at the net loss available to common stockholders in the calculation of net loss per common share. All redeemable convertible preferred stock shares were converted into common stock as of the date of the Company's IPO.

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.

Segments

The Company has one reporting segment which is also the Company's only operating segment. Management uses one measurement of profitability and does not segregate its business for internal reporting. All long-lived assets are maintained in the United States.

Recently Adopted Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued ASU No. 2016-02 titled *Leases* ("ASU 2016-02"), which requires rights and obligations arising from both operating and capital leases to be reported on the Consolidated Balance Sheet, and to disclose quantitative and qualitative information about lease transactions (such as information about variable lease payments and options to renew and terminate leases). ASU 2016-02 was effective for fiscal years beginning after December 15, 2018, with early adoption permitted.

The Company adopted this new guidance as of January 1, 2019, which included an assessment of the impact of the new guidance on the Consolidated Financial Statements. The Company utilized the transition practical expedient added by the FASB, which eliminated the requirement that entities apply the new lease standard to the comparative periods presented in the year of adoption. The Company elected to use the package of practical expedients that allowed the Company to not reassess: (1) whether any expired or existing contracts were or contained leases, (2) lease classification for any expired or existing leases and (3) initial direct costs for any expired or existing leases. The Company additionally used the practical expedient that allows lessees to treat the lease and non-lease components of leases as a single lease component. The adoption of this standard resulted in the recognition of a right-of-use asset of $379 and related lease liabilities of $424 related to the Company's operating lease commitments on the Consolidated Balance Sheet as of January 1, 2019 *(Note 4)*. The impact of adoption of the new leasing standard did not have a material impact on the Consolidated Statement of Operations during year ended December 31, 2019.

Recently Issued Accounting Pronouncements

In December 2019, the FASB issued ASU 2019-12, *Simplifying the Accounting for Income Taxes*. The list of changes is comprehensive and many will not have a significant effect on the Company's consolidated financial reporting. The changes include removing exceptions to incremental intraperiod tax allocation of losses and gains from different financial statement components, exceptions to the method of recognizing income taxes on interim period losses and exceptions to deferred tax liability recognition related to foreign subsidiary investments. In addition, ASU 2019-12 requires that entities recognize franchise tax based on an incremental method, requires an entity to evaluate the accounting for step-ups in the tax basis of goodwill as inside or outside of a business combination, and removes the requirement to allocate the current and deferred tax provision among entities in stand-alone financial statement reporting. ASU 2019-12 also now requires that an entity reflect enacted changes in tax laws in the annual effective rate, and other codification adjustments have been made to employee stock ownership plans. For public business entities, the amendments in ASU 2019-12 are effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020. Early adoption of ASU 2019-12 is permitted, including adoption in any interim period for public business entities for periods for which financial statements have not yet been issued. An entity that elects to early adopt the amendments in an interim period should reflect any adjustments as of the beginning of the annual period that includes that interim period. Additionally, an entity that elects early adoption must adopt all the amendments in the same period. The Company is currently evaluating whether to early adopt ASU 2019-12 in the first interim period of the year ending December 31, 2020.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments — Credit Losses (Topic 326), Measurement of Credit Losses on Financial Instruments*, which changes the way credit losses on certain financial instruments are estimated. ASU 2016-13 is effective for fiscal years beginning after December 15, 2019, with early adoption permitted. The Company does not expect that the adoption of ASU 2016-13 will have a material effect on its Consolidated Financial Statements.

3. Prepaid Expenses

Prepaid expenses consist of the following:

	As of December 31,	
	2019	2018
Prepaid R&D payments	$ 1,113	$ 1,337
Prepaid corporate insurance	491	59
Other	77	42
	$ 1,681	$ 1,438

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 was 13.0% as of December 31, 2019. The right-of-use asset also includes any 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 year ended December 31, 2019.

The Company's operating leases consist of real estate and equipment, and have remaining terms ranging from approximately 1 to 3 years. The Company has no financing leases. The following table summarizes the Company's operating leases as presented on its Consolidated Balance Sheet as of December 31, 2019:

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

Future minimum lease payments under the operating leases are as follows as of December 31, 2019:

	As of December 31, 2019
2020	$ 138
2021	138
2022	131
2023	24
Total lease payments	431
Less: imputed discount	(75)
Carrying value of operating lease liabilities	$ 356

Lease expense under operating leases, including leases of office equipment, was $124 and $112 for the years ended December 31, 2019 and 2018, respectively. Lease payments made were $125 and $117 in the years ended December 31, 2019 and 2018 respectively, with such amounts reflected in the Consolidated Statement of Cash Flows in operating activities.

5. Property, Equipment and Leasehold Improvements, Net

Property, equipment and leasehold improvements, net consist of the following:

	As of December 31,	
	2019	2018
Computer, website development and office equipment	$ 45	$ 47
Furniture and fixtures	28	18
Leasehold improvements	130	130
	203	$ 195
Less accumulated depreciation	(85)	(46)
	$ 118	$ 149

Depreciation was $39 and $23 for the years ended December 31, 2019 and 2018, respectively.

6. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
	2019	2018
Accrued research projects	$ 2,084	$ 942
Accrued professional fees	338	477
Accrued compensation and benefits	776	584
Other	303	70
	$ 3,501	$ 2,073

7. 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 December 31, 2019 or 2018, 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 December 31, 2019. The total fair value of these liabilities was determined to be $460 at December 31, 2018. The Company recorded non-cash charges in the amount of $215 and $138 for the years ended December 31, 2019 and 2018, respectively, representing the changes in the fair value of these liabilities since their last measurement date. The non-cash charges are included in other income (expense) in the Company's Consolidated Statements of Operations. The obligation for the Success Fee is presented as a non-current liability in the Company's Consolidated Balance Sheet as of December 31, 2018.

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. For the fair value calculations at December 31, 2018, significant inputs included the Success Fee rate of 4.5% of the Term Loan funded; a discount rate of 13.0%; weighted estimated time to Exit Event ranging from 0.4 to 3.1 years and probability estimates of several potential Exit Events ranging from 5.0% to 40.0%.

Interest expense on the Term Loan, comprised of interest payments, amortization of financing costs, accrual of final and amendment fees, and accretion of the Success Fee are shown below for the year ended December 31, 2018. There was no such interest expense on the Term Loan for the year ended December 31, 2019.

	Year Ended December 31, 2018
Interest payments	$ 114
Amortization of financing costs	19
Accrual of final and amendment fees	24
Accretion of the Success Fee	17
	$ 174

8. Common Stock

As of December 31, 2019 and 2018, the Company's certificate of incorporation, as amended and restated, authorized the Company to issue 200,000,000 shares and 101,929,904 shares of common stock, respectively, with a par value of $0.001 per share.

As of December 31, 2019, the Company had reserved 2,778,812 shares of common stock 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. As of December 31, 2018, the Company had reserved 10,690,261 shares of common stock for the conversion of outstanding shares of redeemable convertible preferred stock and accrued dividends thereon, 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 as shown below (*Note 10*):

	As of December 31,	
	2019	2018
Shares of common stock reserved for conversion of Series A preferred stock outstanding	—	2,154,572
Shares of common stock reserved for conversion of Series B preferred stock outstanding	—	3,011,392
Shares of common stock reserved for conversion of Series C preferred stock outstanding	—	4,311,279
Shares of common stock reserved for future issuance under the 2012 Stock Incentive Plan	1,043,992	1,213,018
Shares of common stock reserved for future issuance under the 2019 Stock Incentive Plan	1,579,714	—
Shares of common stock reserved for future issuance under the 2019 Employee Stock Purchase Plan	155,106	—
	2,778,812	10,690,261

9. Redeemable Convertible Preferred Stock

As of December 31, 2019 and 2018, under the Company's certificate of incorporation, the authorized number of shares of redeemable convertible preferred stock was 0 and 86,197,030, respectively. See Note 1 with respect to the Company's IPO and the conversion of its outstanding redeemable convertible preferred stock into shares of its common stock.

As of December 31, 2019 and 2018, under the Company's restated certificate of incorporation effective May 9, 2019, the authorized number of shares of preferred stock was 5,000,000 and 0, respectively.

Prior to the conversion into common stock as noted above, the Company's redeemable convertible preferred stock was redeemable on or after July 14, 2020 and carried a cumulative coupon dividend rate of 6%. The redemption amount per share for a share of redeemable convertible preferred stock was the greater of (A) the applicable original issue price per share for such series of redeemable convertible preferred stock, plus any of the dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon, and (B) the fair market value per share of redeemable convertible preferred stock, as described below under *Redemption Rights.* The Company accounted for its redeemable convertible preferred stock under the requirements of ASC 480, which establishes standards for how an issuer classifies and measures certain financial instruments with characteristics of both liabilities and equity. The carrying value of the redeemable convertible preferred stock was presented as temporary equity and was adjusted by periodic accretions so that the carrying amount equaled the redemption amount at the estimated date that the redeemable convertible preferred stock would be redeemed. These adjustments were effected through charges against additional paid-in capital, to the extent it was available, or accumulated deficit. For all issuances of redeemable convertible preferred stock, the difference between the amount invested by the holders of the redeemable convertible preferred stock, net of issuance costs and premiums (or discounts), as compared to the redemption value, was recorded as accretion over the redemption period of the redeemable convertible preferred stock. The accretion was added to net loss to arrive at the net loss available to common stockholders in the calculation of net loss per common share.

Issuance of Series A Redeemable Convertible Preferred Stock

On December 4, 2012, the Company entered into the Series A Preferred Stock Purchase Agreement (the "Series A Purchase Agreement") with TPG Biotechnology Partners III, L.P. ("TPG") and nine other holders of the Company's convertible notes that were issued in 2011 and 2012 (the "Series A Investors"). Pursuant to the Series A Purchase Agreement, the Company issued 6,000,000 shares (the "Series A Initial Closing") of Series A Preferred Stock to TPG at a purchase price of $1.00 per share, resulting in proceeds, net of $128 in issuance costs, of $5.9 million (the "Series A Financing"). Concurrently, convertible notes held by the Series A Investors totaling $564, including accrued interest, were automatically converted at a conversion price of $0.467 per share in accordance with calculations specified in the applicable note purchase agreement, and the Company issued 1,207,923 shares of Series A Preferred Stock in settlement of the convertible notes.

The Series A Purchase Agreement also provided for the sale of 4,000,000 additional shares of Series A Preferred Stock (the "Series A Milestone Shares") to TPG at a purchase price of $1.00 per share upon the Company's achievement of specified Milestone Events, as defined in the Series A Purchase Agreement, involving the Company's Phase 1b clinical trial in uremic pruritus and a pending patent application. In the event the Milestone Events were not achieved, TPG had the right to purchase the Series A Milestone Shares, in full or in part, under the same terms and conditions as the Series A Initial Closing, including the $1.00 per share purchase price, on or before June 30, 2014.

In addition, TPG had the right to purchase, under the same terms and conditions as the Series A Initial Closing, including the $1.00 per share purchase price, the lesser of 2,500,000 additional shares of Series A Preferred Stock (the "Additional Series A Preferred Shares") and the number of shares of Series A Preferred Stock equal to 25% of the total number of shares of Series A Preferred Stock it previously purchased for cash under the Series A Purchase Agreement. This additional right was exercisable until the date six months after the completion date of the Company's Phase 2b/3 clinical trial of nalbuphine ER in patients with uremic pruritus.

On December 26, 2013, TPG purchased under a Series A Extension Preferred Stock Purchase Agreement (the "Series A Extension Purchase Agreement") 6,500,000 additional shares of Series A Preferred Stock at $1.00 per share, which consisted of the Series A Milestone Shares and the Additional Series A Preferred Shares discussed above, resulting in proceeds, net of $39 in issuance costs, of $6.5 million. This agreement also provided that the Company could sell up to 2,000,000 additional shares at $1.00 per share to existing stockholders deemed accredited investors within 45 days of the December 26, 2013 closing.

In January 2014, the Company issued 1,680,000 shares of Series A Preferred Stock to eight of the Series A Investors at $1.00 per share, as provided for as Additional Closings under the Series A Extension Purchase Agreement, resulting in proceeds, net of $7 in issuance costs, of $1.7 million. The Company recorded this issuance at its fair value of $1.08 per share, totaling $1.8 million before financing costs, resulting in a discount on this issuance in the amount of $134, which amount was being amortized out of the carrying value of Series A Preferred Stock over the expected redemption period, which was three years from July 14, 2017, the date of the First Tranche Closing of the Series C Preferred Stock Financing (each such term as defined below), or July 14, 2020 (the "Redemption Period"). Such amortization totaled $7 and $4 for the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019, includes $5 of previously unaccreted discount on issuance at the time of conversion to shares of common stock.

Holders of Series C Preferred Stock had a higher liquidation preference than the holders of Series A Preferred Stock and Series B Preferred Stock. *(See Liquidation Preferences note below.)*

Issuance of Series B Redeemable Convertible Preferred Stock

On May 23, 2014, the Company entered into the Series B Preferred Stock Purchase Agreement (the "Series B Purchase Agreement") with TPG. Pursuant to the Series B Purchase Agreement, the Company issued 13,043,478 shares (the "Series B Initial Closing") of Series B Preferred Stock to TPG at a purchase price of $1.15 per share, resulting in proceeds, net of $56 in issuance costs, of $15.0 million.

The Series B Purchase Agreement also provided for the sale of 4,347,826 additional shares of Series B Preferred Stock (the "Series B Milestone Shares") to TPG at a purchase price of $1.15 per share upon the Company's achievement of specified Milestone Events, as defined in the Series B Purchase Agreement, involving the Company's Phase 2b/3 clinical trial of nalbuphine ER in patients with uremic pruritus; its planned Phase 2 clinical trial of nalbuphine ER in patients with pruritus associated with prurigo nodularis; and a pending patent application. In the event the Milestone Events were not achieved, TPG had the right to purchase the Series B Milestone Shares, in full or in part, under the same terms and conditions as the Series B Initial Closing, at a purchase price of $1.15 per share, on or before November 30, 2015.

In addition, TPG had the right to purchase, on the same terms and conditions as the Series B Initial Closing, including the $1.15 per share purchase price, the lesser of 4,347,826 additional shares of Series B Preferred Stock and the number of shares equal to 25% of the total number of shares it previously purchased for cash under the Series B Purchase Agreement (the "Additional Series B Shares"). This additional right was exercisable until the date six months after the completion date of the Company's Phase 2b/3 clinical trial of nalbuphine ER in patients with uremic pruritus.

On October 30, 2014, TPG exercised its rights described above and purchased under an Additional Closing Agreement (the "Series B Second Closing") 8,695,652 additional shares of Series B Preferred Stock at $1.15 per share, which consisted of the Series B Milestone Shares and the Additional Series B Shares. This agreement also provided for the Company to sell 869,565 additional shares of Series B Preferred Stock at $1.15 per share to an existing stockholder. The Series B Second Closing resulted in proceeds, net of $19 in issuance costs, of $11.0 million. The Company recorded this issuance at its fair value of $1.10 per share, totaling $10.5 million, net of financing costs, resulting in a premium on this issuance in the amount of $478, which amount was being accreted into the carrying value of the Series B Preferred Stock over the Redemption Period. Such accretion totaled $31 and $20 for the years ended December 31, 2019 and 2018, respectively, which includes $22, for the year ended December 31, 2019 of unaccreted premium on issuance at the time of conversion to shares of common stock.

Holders of Series C Preferred Stock had a higher liquidation preference than the holders of Series A Preferred Stock and Series B Preferred Stock. *(See Liquidation Preferences note below.)*

Issuance of Series C Redeemable Convertible Preferred Stock

On July 14, 2017, the Company entered into the Series C Purchase Agreement with TPG and other institutional investors (the "Series C Initial Purchasers") for the issuance of $50.5 million of its Series C Preferred Stock. The Series C Purchase Agreement provided for the Company's Series C Preferred Stock to be issued in two tranches, with the closing of the first tranche on July 14, 2017 (the "First Tranche Closing") and the closing of the second tranche to occur following a determination by the Company's board of directors that the Company's cash and cash equivalents at such time are not sufficient to fund its operations for a period of three months following such determination (the "Second Tranche Closing"). Upon the First Tranche Closing, the Company issued 20,547,946 shares of its Series C Preferred Stock at a purchase price of $1.46 per share, resulting in proceeds of $29.7 million, net of issuance costs of $291.

Also party to the Series C Purchase Agreement were eleven holders of the Company's Convertible Notes (together with the Initial Purchasers and the Series C Additional Purchasers, as defined below, the "Series C Investors"). Concurrently with the First Tranche Closing and pursuant to the Series C Purchase Agreement, the outstanding principal on the Company's Convertible Notes, totaling $10.6 million, and all accrued interest thereon, totaling $564, were automatically converted at the Mandatory Conversion Price of $1.095 per share, and the Company issued 10,181,233 shares of its Series C Preferred Stock in full settlement of the Convertible Notes.

The Series C Purchase Agreement provided for a subsequent closing (the "Special Closing"), on the same terms and conditions as the First Tranche Closing, including the $1.46 per share purchase price, and on October 11, 2017, the Special Closing occurred, resulting in the issuance to two additional investors (the "Series C Additional Purchasers") of 101,707 shares of the Company's Series C Preferred Stock, at a purchase price of $1.46 per share, resulting in proceeds of $129, net of issuance costs of $19.

On November 12, 2017, one of the Series C Additional Purchasers purchased its second tranche shares pursuant to an election under the Series C Purchase Agreement, resulting in the issuance of 55,621 shares of the Company's Series C Preferred Stock at a purchase price of $1.46 per share, resulting in proceeds of $81.

On August 28, 2018, the Company amended the Series C Purchase Agreement to provide that a portion of the shares of Series C Preferred Stock that would otherwise be issued and sold at the Second Tranche Closing would instead be issued and sold at a third tranche closing (the "Third Tranche Closing"), with such closing to occur following a determination by the Company's board of directors that the Company's cash and cash equivalents at such time are not sufficient to fund its operations for a period of three months following such determination.

On August 30, 2018, the Company completed the Second Tranche Closing, resulting in the issuance of 7,211,165 shares of the Company's Series C Preferred Stock, at a purchase price of $1.46 per share, resulting in proceeds of $10.5 million, net of issuance costs of $32.

On January 18, 2019, the Company completed the Third Tranche Closing, resulting in the issuance of 6,849,315 shares of the Company's Series C Preferred Stock, at a purchase price of $1.46 per share, resulting in proceeds of $10.0 million, net of issuance costs of $37. At such time, the Series C redeemable convertible preferred stock liability of $1.1 million was reclassified as Series C Preferred Stock.

Series C Redeemable Convertible Preferred Stock Liability and Changes in Fair Value

As discussed above, the Series C Purchase Agreement provided for the issuance and sale of Series C Preferred Stock in three separate tranches. The tranches represented a freestanding financial instrument under ASC 480 and required fair value accounting until they were settled. The Company recognized a liability on its Consolidated Balance Sheet for the obligations under this financial instrument. The Company adjusted this liability to fair value at each reporting date, as applicable, and recognized any changes in fair value of the Series C Preferred Stock in its Consolidated Statements of Operations as a component of other income (expense). The Company continued to recognize any changes in the fair value of this liability through the closing of the third tranche.

Accordingly, for the year ended December 31, 2018, the Company recorded the Series C redeemable convertible preferred stock liability at its fair value of $2.1 million, with a corresponding charge to other income (expense) in the Company's Consolidated Statement of Operations. Upon the Second Tranche Closing in August 2018, as described above, $1.0 million was reclassified to Series C Preferred Stock. As a result, at December 31, 2018, the fair value of this liability, relating to the outstanding third tranche, was determined to be $1.1 million and was reclassified to Series C Preferred Stock upon the Third Tranche Closing in January 2019.

The fair value of the Series C redeemable convertible preferred stock liability was estimated as the excess, if any, of the fair value per share of the Company's Series C Preferred Stock, as described below under *Redemption Rights*, over the purchase price of any outstanding tranches to be sold pursuant to the Series C Purchase Agreement.

Holders of Series C Preferred Stock had a higher liquidation preference than the holders of Series A Preferred Stock and Series B Preferred Stock. *(See Liquidation Preferences note below.)*

As of December 31, 2019, there were no shares of redeemable convertible preferred stock outstanding as a result of the conversion into common stock in connection with the IPO. As of December 31, 2018, redeemable convertible preferred stock consisted of the following (in thousands, except share amounts).

	As of December 31, 2018				
	Preferred Shares Authorized	Preferred Shares Issued and Outstanding	Carrying Value	Liquidation Preference	Common Shares Issuable Upon Conversion
Series A redeemable convertible preferred stock	15,387,923	15,387,923	$ 21,033	$ 20,469	2,154,572
Series B redeemable convertible preferred stock	22,608,695	22,608,695	33,686	32,900	3,011,392
Series C redeemable convertible preferred stock	48,200,412	38,097,672	61,023	59,798	4,311,279
	86,197,030	76,094,290	$ 115,742	$ 113,167	9,477,243

Dividends

Dividends on outstanding shares of Series A, Series B and Series C Preferred Stock accrued at a rate of 6% per annum on their original purchase price of $1.00, $1.15 and $1.46 per share, respectively (the "Accruing Dividends"), whether or not declared, and were cumulative. However, Accruing Dividends on the Company's outstanding redeemable convertible preferred stock were payable only when, as and if declared by the Company's board of directors, or upon liquidation, redemption or conversion. No dividends were payable to the holders of the Company's common stock unless equivalent dividends had been declared and paid on the Company's outstanding Series A, Series B and Series C Preferred Stock. No dividends had been declared or paid by the Company through the date of the IPO. Accruing Dividends totaled $18.4 million through the date of the IPO, at which time they were converted into common shares. Accruing Dividends totaled $16.2 million as of December 31, 2018. Such amounts are included in the carrying values of Series A, Series B and Series C Preferred Stock, and in the accumulated deficit on the Company's Consolidated Balance Sheet at December 31, 2018.

Liquidation Preferences

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, the holders of shares of Series C Preferred Stock then outstanding were entitled to be paid out of the assets of the Company that were available for distribution to its stockholders, before any payments were to be made to the holders of Series A Preferred Stock, Series B Preferred Stock or common stock by reason of their ownership thereof, an amount per share equal to the Series C Preferred Stock original issue price of $1.46 per share, plus any Accruing Dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon. If upon any such liquidation, dissolution or winding up of the Company or deemed liquidation event, the assets of the Company available for distribution to its stockholders were insufficient to pay the holders of shares of Series C Preferred Stock the full amount to which they were entitled, the holders of Series C Preferred Stock were entitled to share ratably in any distribution of the assets available for distribution in proportion to the respective amounts which would otherwise be payable in respect of the shares of Series C Preferred Stock held by them upon such distribution if all amounts payable on or with respect to such shares were paid in full.

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, the holders of shares of Series A Preferred Stock and Series B Preferred Stock then outstanding were entitled to be paid out of the assets of the Company available for distribution to its stockholders after the payment of all preferential amounts required to be paid to the holders of shares of Series C Preferred Stock but before any payments were made to the holders of common stock by reason of their ownership thereof, (i) an amount per share equal to the Series A original issue price of $1.00 per share in the case of the Series A Preferred Stock, plus any Accruing Dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon, and (ii) an amount per share equal to the Series B original issue price of $1.15 per share in the case of the Series B Preferred Stock, plus any Accruing Dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon. If upon any such liquidation, dissolution or winding up of the Company or deemed liquidation event, the assets of the Company available for distribution to its stockholders were insufficient to pay the holders of shares of Series A Preferred Stock and Series B Preferred Stock the full amount to which they were entitled (after the payment in full of all preferential amounts required to be paid to the holders of shares of Series C Preferred Stock), the holders of shares of Series A Preferred Stock and Series B Preferred Stock were entitled to share ratably in any distribution of the assets available for distribution in respect of such shares in proportion to the respective amounts which would otherwise be payable in respect of the share of Series A Preferred Stock and Series B Preferred Stock held by them upon such distribution if all amounts payable on or with respect to such shares were paid in full.

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, after the payment of all preferential amounts required to be paid to the holders of shares of redeemable convertible preferred stock, the remaining assets of the Company available for distribution to its stockholders were to be distributed among the holders of the shares of redeemable convertible preferred stock and common stock, in proportion to the number of shares held by each such holder, treating for this purpose all such securities as if they had been converted into common stock pursuant to the terms of the Company's certificate of incorporation immediately prior to such dissolution, liquidation or winding up of the Company.

Redemption Rights

The Company's certificate of incorporation provided that, unless prohibited by Delaware law governing distributions to stockholders, shares of the redeemable convertible preferred stock were to be redeemed by the Company in three annual installments commencing not more than 60 days after receipt by the Company, at any time on or after July 14, 2020, of written notice from the holders of at least a majority of the outstanding shares of redeemable convertible preferred stock, voting together as a single class on an as-converted basis, requesting redemption of all shares of redeemable convertible preferred stock (a "Redemption Request").

In that event, unless prohibited by Delaware law governing distributions to stockholders, generally in connection with an insolvent corporation, shares of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock, respectively, were to be redeemed by the Company at a price equal to the greater of (A) the applicable original issue price per share for such series of redeemable convertible preferred stock, plus any Accruing Dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon, and (B) the fair market value per share of Series A Preferred Stock, Series B Preferred Stock or Series C Preferred Stock, as the case may be, as of the date of the Company's receipt of the Redemption Request. For purposes of these redemption rights, the fair market value per share of the Series A Preferred Stock was defined as the value per share of Series A Preferred Stock as mutually agreed upon by the Company and the holders of 60% of the shares of Series A Preferred Stock then outstanding, and, in the event that they were unable to reach agreement, by a third-party appraiser agreed to by the Company and the holders of a majority of the shares of Series A Preferred Stock then outstanding; the fair market value per share of the Series B Preferred Stock was defined as the value per share of Series B Preferred Stock as mutually agreed upon by the Company and the holders of 60% of the shares of Series B Preferred Stock then outstanding, and, in the event that they were unable to reach agreement, by a third-party appraiser agreed to by the Company and the holders of a majority of the shares of Series B Preferred Stock then outstanding; and the fair market value per share of the Series C Preferred Stock was defined as the value per share of Series C Preferred Stock as mutually agreed upon by the Company and the holders of 66 2/3% of the shares of Series C Preferred Stock then outstanding, and, in the event that they were unable to reach agreement, by a third-party appraiser agreed to by the Company and the holders of a majority of the shares of Series C Preferred Stock then outstanding.

As a result of the redemption rights described above, the carrying values of Series A Preferred Stock of $21.0 million, Series B Preferred Stock of $33.7 million, and Series C Preferred Stock of $61.0 million as of December 31, 2018, have been classified as temporary equity, and are presented between liabilities and stockholders' equity (deficit) on the Company's Consolidated Balance Sheets in accordance with ASC 480. The Company was accreting the carrying value of the redeemable convertible preferred stock up to the expected redemption value over the estimated Redemption Period. The accretion included cumulative unpaid and undeclared Accruing Dividends as well as additional increases, if any, when the fair value of the redeemable convertible preferred stock exceeded the liquidation value at any point during the Redemption Period. Upon the IPO, all redeemable convertible preferred shares and Accruing Dividends thereon converted to common shares and all previously unaccreted amounts were fully accreted to the expected redemption value.

At December 31, 2018, the fair values of the Company's Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock were determined utilizing a probability-weighted modeling approach that included both IPO and non-IPO based scenarios. The non-IPO based scenarios included the fair value estimates of the Company's common stock, before marketability discount, of $0.47, and each issue of its redeemable convertible preferred stock of: $0.82 for its Series A Preferred Stock; $0.86 for its Series B Preferred Stock; and $1.44 for its Series C Preferred Stock, each calculated at December 31, 2017, as there were no clinical development milestones either achieved or not achieved during the period, and it was deemed that the Company's total equity value had not changed to any significant degree through the December 31, 2018 measurement date. Additional significant inputs utilized for the non-IPO based scenario was a probability factor of 60% and a marketability discount of 20% applied in arriving at the fair value of the common stock. The IPO-based scenario utilized an expected pre-money valuation upon IPO; cost of equity estimate of 15%; estimated time to IPO date of 0.38 years; and a probability factor of 40%.

At December 31, 2017, the fair value of the Company's Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock was determined utilizing the OPM; whereby each class of stock is modeled as a call option with a unique claim on the assets of the Company. Stock characteristics that were incorporated directly into the option valuation model include liquidation preferences, participation features, convertibility features and ratios, and value-sharing between classes of stock. The Company's equity value was estimated by employing a back-solving approach to determine its implied equity value at December 31, 2017 based on the initial closing of the Series C Preferred Stock financing completed in July 2017. A Black-Scholes options pricing approach was utilized under the OPM to determine the fair value of each security, with significant inputs including a $1.44 fair value of the Series C Preferred Stock, a risk-free rate of 1.95%, volatility of 78.0% and a probability-weighted estimate of time to liquidity event of 2.71 years.

Financing costs of approximately $166 that were netted against the proceeds from the 2013 and 2012 Series A Preferred Stock financings were being accreted to Series A Preferred Stock over the period from their respective issuance dates to the earliest redemption date of July 14, 2020. The Company recorded $7 and $5 in accretion for financing costs for the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019 includes $5 of previously unaccreted financing costs at the time of the conversion of the Series A Preferred Stock into shares of the Company's common stock. In addition, the investor rights/obligation that was allocated from proceeds from the Series A Preferred Stock financings of $2.8 million, less $520 representing its fair value on the date of its exercise as noted above, was being accreted over the Redemption Period. The Company recorded $84 and $54 in accretion of investor rights/obligation in the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019 includes $61 of previously unaccreted investor rights/obligations at the time of the conversion of the Series A Preferred Stock into shares of the Company's common stock.

Financing costs of approximately $76 that were netted against the proceeds from the 2014 Series B Preferred Stock financings were being accreted to Series B Preferred Stock over the period from their respective issuance dates to the earliest redemption date of July 14, 2020. The Company recorded $4 and $3 in accretion for financing costs in the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019 includes $3 of previously unaccreted financing costs at the time of conversion of the Series B Preferred Stock into shares of the Company's common stock. In addition, the investor rights/obligation that was allocated from proceeds from the Series B Preferred Stock financings of $2.0 million was being accreted over the remaining Redemption Period discussed above. The Company recorded $117 and $76 in accretion of Series B Preferred Stock investor rights/obligation in the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019 includes $85 of previously unaccreted investor rights/obligations at the time of the conversion of the Series B Preferred Stock into shares of the Company's common stock.

Financing costs of approximately $379 that were netted against the proceeds from the 2017, 2018 and 2019 Series C Preferred Stock financings were being accreted to Series C Preferred Stock over the period from their respective issuance dates to the earliest redemption date of July 14, 2020. The Company recorded $223 and $109 in accretion for financing costs in the years ended December 31, 2019 and 2018, respectively, which, for the year ended December 31, 2019 includes $164 of previously unaccreted financing costs at the time of conversion of the Series C Preferred Stock into shares of the Company's common stock.

Optional Conversion

Each holder of Series A, Series B or Series C Preferred Stock was able to convert any or all of such holder's redeemable convertible preferred stock into common stock at any time. Each share of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock was convertible into such number of shares of common stock as determined by dividing the original issue price of such series by the conversion price for such series in effect at the time of conversion. As of December 31, 2018, each share of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock was convertible into common stock at a one-to-one conversion ratio. As of December 31, 2019, there were no redeemable convertible preferred shares outstanding as a result of the conversion into common shares in connection with the IPO.

In addition, upon conversion of shares of Series A, Series B or Series C Preferred Stock, a holder was entitled to receive, at the election of the holder, either (i) payment in cash of any Accruing Dividends declared but unpaid thereon, or (ii) such number of shares of common stock as determined by dividing the Accruing Dividends for such share of Series A, Series B or Series C Preferred Stock, by the applicable conversion price for such series of redeemable preferred stock in effect at the time of conversion. The conversion prices for Series A, Series B or Series C Preferred Stock were subject to adjustment based on certain events specified in the Company's certificate of incorporation, including anti-dilution adjustments.

Mandatory Conversion

Upon the closing of a qualified public offering of common stock, as defined in the Company's certificate of incorporation, or approval of (i) the holders of at least 60% of the Series A Preferred Stock then outstanding, voting separately as a class, (ii) the holders of at least 60% of the Series B Preferred Stock then outstanding, voting separately as a class and (iii) the holders of at least 66 2/3% of the Series C Preferred Stock then outstanding, voting separately as a class, all outstanding shares of redeemable convertible preferred stock would have automatically converted into common stock at the then-applicable conversion rate for such shares. At December 31, 2019, there were no redeemable convertible preferred shares outstanding as a result of the conversion into common shares at a one-for-9.5 conversion ratio, in connection with the IPO.

Voting Rights

Prior to the IPO, and except as otherwise provided by law or by the other provisions of the Company's certificate of incorporation, the holders of redeemable convertible preferred stock were entitled to vote as one class with the holders of common stock on any matter presented to the stockholders of the Company for their action or consideration at any meeting of stockholders of the Company (or by written consent of stockholders in lieu of a meeting), and each holder of outstanding shares of redeemable convertible preferred stock was entitled to cast the number of votes equal to the number of whole shares of common stock into which the shares of redeemable convertible preferred stock held by such holder were convertible as of the record date for determining stockholders entitled to vote on the matter. The holders of record of the shares of the Company's Series B Preferred Stock, exclusively and as a separate class, were entitled to elect two directors of the Company, the holders of record of the shares of Series C Preferred Stock, exclusively, and as a separate class, were entitled to elect three directors of the Company, and the holders of record of the shares of common stock of the Company, exclusively and as a separate class, were entitled to elect two directors of the Company.

Registration Rights

The holders of shares of the Company's common stock issued upon conversion of shares of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock have certain registration rights as set forth in an investors' rights agreement between the Company and certain of its stockholders.

10. 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.

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 2012 Plan 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 Company's 2012 Stock Incentive Plan (the "2012 Plan"), as amended, 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 December 31, 2019, options to purchase 631,234 shares of common stock were granted and outstanding, net of cancelations, under the 2019 Plan. As of December 31, 2019 and 2018, respectively, options to purchase 1,043,992 and 1,077,148 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.

A summary of the Company's combined stock option activity for the 2019 Plan and the 2012 Plan for the year ended December 31, 2019 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, 2018	1,077,148	$ 3.90	7.8	$ 5,857
Granted	678,602	9.99		
Forfeited	(59,429)	8.60		
Expired	(6,359)	3.08		
Exercised	(14,736)	2.60		
Outstanding as of December 31, 2019	1,675,226	$ 6.20	7.8	$ 864
Options exercisable as of December 31, 2019	695,454	$ 3.17	6.1	$ 771
Options unvested as of December 31, 2019	979,772	$ 8.35	9.0	$ 93

The weighted average grant-date fair value per share of stock options granted was $5.06 and $4.85 for the years ended December 31, 2019 and 2018, respectively.

The aggregate fair value of stock options that vested during the years ended December 31, 2019 and 2018 was $688 and $336, respectively.

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2019 and 2018 was $105 and $6, respectively.

The assumptions that the Company used to determine the fair value of the stock options granted were as follows, presented on a weighted average basis:

	Year Ended December 31,	
	2019	2018
Risk-free interest rate	2.0%	2.7%
Expected volatility	78.7%	70.2%
Expected dividend yield	—	—
Expected life of options (in years)	6.0	6.0

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

	Year Ended December 31,	
	2019	2018
Research and development expense	$ 143	$ 159
General and administrative expense	984	337
	$ 1,127	$ 496

As of December 31, 2019, total unrecognized compensation cost related to the unvested share-based awards was $3.9 million, which is expected to be recognized over a weighted average period of 3.0 years.

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 December 31, 2019, there has been no activity under the 2019 ESPP.

The number of shares of the Company's common stock that have been approved 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.

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.

11. Income Taxes

During the years ended December 31, 2019 and 2018, the Company recorded an income tax benefit related to state research and development tax credits of $18 and $124, respectively.

The components of income tax (benefit) for the years ended December 31, 2019 and 2018, are as follows:

	Year Ended December 31,	
	2019	2018
Current:		
Federal	$ —	$ —
State	(18)	(124)
	$ (18)	$ (124)
Deferred:		
Federal	—	—
State	—	—
	—	—
Income tax (benefit)	$ (18)	$ (124)

A reconciliation between income tax benefit and the expected tax benefit at the statutory rate for the years ended December 31, 2019 and 2018 is as follows:

	Year Ended December 31,	
	2019	2018
Federal statutory income tax rate	21.0%	21.0%
State income tax (benefit)—net of federal tax	5.9	5.4
Permanent differences	—	(2.3)
Change in valuation allowance	(28.2)	(27.6)
Refundable tax credit	0.1	0.6
R&D tax credits	1.4	3.5
Lease Standard Adoption	(0.1)	—
Effective income tax rate	0.1%	0.6%

Significant components of the Company's deferred tax assets are as follows:

	Year Ended December 31,	
	2019	2018
Net operating loss carryforwards	$ 28,745	$ 22,325
Federal and state tax credits	3,350	2,979
Other	1,200	631
	33,295	25,935
Valuation allowance	(33,295)	(25,935)
Net deferred tax asset	$ —	$ —

For the years ended December 31, 2019 and 2018, the Company generated federal and state net operating losses ("NOLs") of approximately $23.9 million and $17.8 million, respectively. At December 31, 2019 and 2018, the Federal and state net operating loss balances were approximately $106.8 million and $82.9 million, respectively. The operating losses generated prior to 2018 will expire in years 2031 through 2037, unless previously utilized. The operating losses generated in 2019 and 2018 can be carried forward indefinitely, however will only offset 80% of taxable income in a carryforward year. The Company also generated federal R&D tax credits in 2019 of approximately $365. At December 31, 2019 and 2018, the federal R&D tax credits were approximately $3.2 million and $2.9 million, respectively. These credits will expire in years 2032 through 2039, unless previously utilized. Due to the Series A preferred stock financing in December 2012 and the shares issued in connection with the Company's IPO in May 2019, the Company was subject to an "ownership change" under the Code Section 382. As a result, the Company's ability to utilize approximately $91.3 million of its NOL carryforwards and approximately $3.0 million of research tax credits is limited.

The Company also generated state research tax credits for the years ended December 31, 2019 and 2018 of approximately $82 and $243, respectively. The Company applied to exchange most of these credits for cash under a state-run program. These amounts, $18 and $124 for the years ended December 31, 2019 and 2018, respectively, were recognized as current income tax benefits in the Company's Consolidated Statements of Operations. At December 31, 2019 and 2018, the Company's Consolidated Balance Sheets reflect income tax receivable of $18 and $124, respectively, related to these credits. Because of the net operating loss and research credit carryforwards, tax years 2011 through 2019 remain open to U.S. federal and state tax examinations.

Income taxes are provided using the asset/liability method, in which deferred taxes are recognized for the tax consequences of temporary differences between the financial statement carrying amounts and tax bases of existing assets and liabilities. The Company reviews deferred tax assets for recoverability on a regular basis. In assessing the need for a valuation allowance, the Company considers both positive and negative evidence related to the likelihood of realization of the deferred tax assets. The weight given to the positive and negative evidence is commensurate with the extent to which the evidence may be objectively verified. Accounting guidance states that a cumulative loss in recent years is a significant piece of negative evidence that is difficult to overcome in determining that a valuation allowance is not needed against deferred tax assets. As such, it is generally difficult for positive evidence regarding projected future taxable income exclusive of reversing taxable temporary differences to outweigh objective negative evidence of recent financial reporting losses.

The Company determined that operating losses it incurred since its inception on March 17, 2011, represented negative evidence sufficient to conclude a valuation allowance was necessary. As such, the Company has recorded a valuation allowance of $33.3 million and $25.9 million at December 31, 2019 and 2018, respectively, as a reserve against its net deferred tax assets. These balances reflect increases in the valuation allowance of $7.4 million and $5.7 million in 2019 and 2018, respectively, both representing an increase in net deferred tax assets.

The Company applies the provisions of ASC 740, which prescribes a comprehensive model for how a company should recognize, measure, present, and disclose in its financial statements uncertain tax positions that the Company has taken or expects to take on a tax return. The financial statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. As a result of the implementation of ASC 740, the Company recognized no adjustment for unrecognized income tax benefits. The Company has not, as of yet, conducted a study of R&D tax credit carryforwards. Such a study could result in an adjustment to the Company's R&D tax credit carryforwards; however, until a study is completed and any potential adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's R&D tax credits and, if an adjustment is required in the future, this adjustment would be offset by a corresponding adjustment to the valuation allowance. For the years ended December 31, 2019 and 2018, the Company had no unrecognized tax benefits or related interest and penalties accrued. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of interest expense.

12. 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:

	As of December 31,	
	2019	2018
Net loss	$ (26,050)	$ (20,545)
Dividends accrued on redeemable convertible preferred stock	(2,239)	(5,402)
Accretion of redeemable convertible preferred stock	1,535	370
Adjusted net loss attributable to common stockholders	$ (26,754)	$ (25,577)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	11,735,781	437,610
Basic and diluted net loss per common share outstanding	$ (2.28)	$ (58.44)

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 December 31, 2019 and 2018, 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 December 31,	
	2019	2018
Series A redeemable convertible preferred stock	—	15,387,923
Series B redeemable convertible preferred stock	—	22,608,695
Series C redeemable convertible preferred stock	—	38,097,672
Outstanding stock options	1,675,226	1,077,148
	1,675,226	77,171,438

13. 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.

14. 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 13).

15. Retirement Plan Other Employee Benefits

Savings Plan

In March 2013, the Company adopted and became a participating employer of a multiple employer defined contribution retirement plan that complies with Section 401(k) of the Code. All eligible employees of the Company immediately participate in the plan (with an entry date of the first day of any month), with no minimum service requirement. The 401(k) plan provides that the Company make non-discretionary matching contributions of 50% of the first 6% of elective contributions. Participants are immediately vested in their contributions, as well as any earnings thereon. Vesting in the employer match contribution portion of their accounts, as well as any earnings thereon, is based on years of credited service, vesting over a four-year period, with 25% vesting per completed year. The Company's expense under the 401(k) plan, representing its employer matching contributions and additional contributions in accordance with regulatory compliance requirements, totaled $111 and $38 in the years ended December 31, 2019 and 2018, respectively.

Health Care and Life Insurance Benefits

The Company offers health care and life insurance benefits to all eligible and active employees. Costs incurred for these benefits totaled $289 and $305 during the years ended December 31, 2019 and 2018, respectively.

Exhibit 4.2

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

As of December 31, 2019, Trevi Therapeutics, Inc. ("we", "us" or the "Company") had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"): our common stock, $0.001 par value per share.

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our our certificate of incorporation, which we refer to as our Certificate of Incorporation; our by-laws, which we refer to as our "By-laws"; and applicable provisions of the Delaware General Corporation Law, or the "DGCL". You should read our Certificate of Incorporation and our By-laws, which are filed as an exhibit to the Annual Report on Form 10-K of which this exhibit is a part, for the provisions that are important to you.

Authorized Capital Stock

Our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.001 per share, and 5,000,000 shares of preferred stock, par value $0.001 per share. Our common stock is registered under Section 12(b) of the Exchange Act.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Each election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding convertible preferred stock.

In the event of our liquidation or dissolution, the holders of our common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any of our outstanding convertible preferred stock. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our convertible preferred stock that we may designate and issue in the future.

Preferred Stock

Under the terms of our certificate of incorporation, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. There are no shares of preferred stock currently outstanding, and we have no present plans to issue any shares of preferred stock.

Provisions of Our Certificate of Incorporation and Bylaws and Delaware Law That May Have Anti-Takeover Effects

Delaware Law

We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless either the interested stockholder attained such status with the approval of our board of directors, the business combination is approved by our board of directors and stockholders in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Exclusive Forum Selection

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, other employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or by-laws (in each case, as they may be amended from time to time) 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. Although our certificate of incorporation contains the choice of forum provisions described above, it is possible that a court could rule that such provisions are inapplicable for a particular claim or action or that such provisions are unenforceable.

Exhibit 10.10

TREVI THERAPEUTICS, INC.
EMPLOYMENT AGREEMENT

This EMPLOYMENT AGREEMENT (the "Agreement") is made and entered into by and between Trevi Therapeutics, Inc., a Delaware corporation (the "Company") and **Thomas R. Sciascia** (the "Executive") as of this 4th day of December, 2012.

W I T N E S S E T H

WHEREAS, the Company and the Executive desire to enter into an employment relationship pursuant to the terms and conditions set forth in this Agreement;

NOW THEREFORE, in consideration of the foregoing, of the mutual promises contained herein and of other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

1. **POSITION/DUTIES**. The terms of this Agreement shall govern the Executive's employment with the Company as Chief Medical Officer, effective December 4th, 2012 (the "Commencement Date"). In this position, the Executive shall report to the Company's Chief Executive Officer (the "CEO") and the Board of Directors of the Company (the "Board") and shall have such duties, authorities and responsibilities as are customary with his position (subject to the control of the Company's CEO and the Board). The Executive agrees to devote his full business time, best efforts, skill, knowledge, attention, and energies to the advancement of the Company's business and interests and to the performance of his duties and responsibilities as an employee of the Company. Notwithstanding the foregoing, the Company agrees that the Executive may serve on such boards of directors as the Board may agree.

2. **BASE SALARY AND BONUS**. The Company agrees to pay the Executive a base salary at the rate of $25,000 per monthly pay period which if annualized equals $300,000 (the "Base Salary"), to be paid in accordance with the Company's normal payroll procedure and policies. Such base salary may be adjusted from time to time in accordance with normal business practices and in the sole discretion of the Company. Following the end of each calendar year that the Executive is employed by the Company, commencing with the calendar year 2012, the Executive may be eligible to receive a discretionary performance bonus of up to thirty percent (30%) of his then current annual Base Salary. The bonus, if any, will be based on both individual and corporate performance goals and will be determined by the Board in its sole discretion. In order to be eligible for a bonus, if any, the Executive must be an active employee of the Company on the date such bonus is distributed. Any bonus payable to the Executive under this Agreement will be paid no later than March 15 of the calendar year following the calendar year in which such bonus is earned and approved by the Board. All compensation payable to the Executive pursuant to this Agreement shall be subject to applicable taxes and withholdings.

3. **BENEFITS/PERQUISITES**.

(a) **Benefit Plans**. The Executive may participate in all benefit programs that the Company establishes and makes available to its employees from time to time, provided that the Executive is eligible under, and subject to the provisions of the plan documents governing those programs. The benefits made available by the Company, and the rules, terms, and conditions for participation in such benefit plans, may be changed by the Company at any time and from time to time without advance notice.

(b) **Vacation and Sick Leave**. The Executive shall be eligible for four weeks of paid vacation per calendar year (as prorated for partial years). The Executive shall also be entitled to sick leave and all Company holidays as determined by the Board, on the same terms as similarly situated senior executives of the Company.

(c) **Business Expenses**. Upon presentation of appropriate documentation, the Executive shall be reimbursed in accordance with the Company's expense reimbursement policy for all reasonable and necessary business expenses incurred in connection with the performance of his duties hereunder. Such business expenses shall include the Executive's reasonable hotel and travel costs associated with his commute to, and performance of services at, the Company's principal corporate offices in Connecticut.

4. **AT WILL EMPLOYMENT**. It is understood that the Executive's employment by the Company shall be on an "at will" basis and may be terminated at the Executive's option or the option of the Company, as the case may be, at any time, for any reason and with or without cause, on the terms and subject to the conditions set forth in this Agreement.

5. **TERMINATION OF EMPLOYMENT AND SEVERANCE BENEFITS**.

(a) **Termination for Cause, by Reason of Death or Disability, or Resignation Other Than for Good Reason**. If the Executive's employment is terminated by the Company for "Cause," as defined below, or by reason of his death or "Disability," as defined below, or if the Executive resigns other than for "Good Reason," as defined below, the Company shall pay or provide to the Executive (or to the Executive's estate or representative) upon such termination or resignation only (i) any accrued but unpaid Base Salary and any vacation time accrued but unused through the date of termination of employment or resignation; (ii) any bonus amount not yet paid that was earned during the calendar year preceding the date of termination of employment or resignation; (iii) reimbursement for any unreimbursed expenses properly incurred and documented through the date of termination of employment or resignation; and (iv) all other payments or benefits to which the Executive may be entitled through the date of his termination of employment or resignation under the terms of any applicable compensation arrangement or plan or by law ((i) to (iv) collectively referred to as the "Accrued Benefits"). Other than the Accrued Benefits, the Executive will not be eligible to receive any severance or any other payments or benefits from the Company following the date of termination of employment or resignation.

(b) **Termination by Company Without Cause or by Executive For Good Reason**. Subject to Section 5(c) below, if the Executive's employment is terminated by the Company without "Cause," as defined below, or if the Executive resigns for "Good Reason," as defined below, then, in exchange for and subject to the Executive's execution and non-revocation of a separation agreement and release of claims in accordance with Section 5(d) below, (a) the Executive will receive as severance pay an amount equal to twelve months of the Executive's then-current base salary (subject to all applicable federal, state and local taxes and withholdings, and payable in accordance with the Company's regular payroll practices) and (b) during such twelve-month severance period, the Company will provide the Executive with medical and dental insurance benefits to the extent the Executive was receiving such benefits prior to such termination and to the extent that the Company is able to provide the Executive with such benefits at a cost to the Company that is not in excess of the cost that the Company was paying for such benefits for the Executive prior to such termination; provided, however, that if the Executive become employed prior to the end of the twelve-month severance period and is eligible to receive medical or dental insurance benefits from the Executive's new employer, then the Company shall no longer be required to provide the Executive with such benefits;

(c) **Termination Following a Change in Control.** If the Executive's employment is terminated by the Company without "Cause," as defined below or if the Executive resigns, whether for "Good Reason" as defined below, or for other than Good Reason, in either case in connection with or within 12 months after a Change In Control, as defined below, then in exchange for and subject to the Executive's execution and non-revocation of a separation agreement and release of claims in accordance with Section 5(d) below, then, in lieu of the severance and benefits contemplated in Section 5(b), (a) the Executive will receive as severance pay an amount equal to twelve months of the Executive's then-current base salary (subject to all applicable federal, state and local taxes and withholdings, and payable in a lump sum) and (b) during a twelve-month severance period commencing at the time set forth in Section 5(d) to the extent necessary to comply with Section 409A of the Internal Revenue Code, the Company will provide the Executive with medical and dental insurance benefits to the extent the Executive was receiving such benefits prior to such termination and to the extent that the Company is able to provide the Executive with such benefits at a cost to the Company that is not in excess of the cost that the Company was paying for such benefits for the Executive prior to such termination; provided, however, that if the Executive become employed prior to the end of the twelve-month severance period and is eligible to receive medical or dental insurance benefits from the Executive's new employer, then the Company shall no longer be required to provide the Executive with such benefits; and

(d) **Conditions to Payment of Severance Benefits**. As a condition of the Executive's receipt of the severance and benefits set forth in Section 5(b) or 5(c) above (the "Severance Benefits"), the Executive must execute and return to the Company a separation agreement and release of claims provided by and satisfactory to the Company (the "Separation Agreement"), and such Separation Agreement must become binding and enforceable within 60 calendar days after the termination of the Executive's employment. The Separation Agreement shall contain, among other things, a general release of claims by the Executive and the agreement of the Executive not to disparage the Company. Payments will be made or commence in the first pay period beginning after the Separation Agreement becomes binding and enforceable, provided that if the foregoing 60 day period would end in a calendar year subsequent to the calendar year in which the Executive's employment ends, payments will not be made or commence before the first payroll period of the subsequent year. The Executive further agrees that, on or prior to his termination or resignation date, the Company may convene an exit interview to review the status of accounts and matters for which the Executive has most recently been responsible to ensure that the Executive is fully entitled to the benefits which may be available under this Agreement and/or to confirm that the Executive clearly understands the nature and scope of all of his post-employment obligations.

In addition, as a condition of the Executive's receipt of the Severance Benefits set forth in Section 5(b) or 5(c) above, the Executive agrees to (i) reasonably cooperate with the Company at its request in all matters relating to the winding up of his pending work on behalf of the Company and the orderly transfer of such work to other employees of the Company following any termination of employment, (ii) during the Severance Period, upon reasonable notice by the Company, make himself reasonably available to the Company on an as-needed basis in connection with the orderly transition of his duties without receiving any additional compensation other than the Severance Benefits, and (iii) reasonably cooperate in the resolution of any dispute (including, without limitation, litigation of any action) involving the Company that relates in any way to the Executive's activities while employed by the Company. The Company shall reimburse the Executive for all reasonable out-of-pocket expenses incurred by the Executive in order to provide such cooperation.

6. **DEFINITIONS**. For the purpose of this Agreement, the following definitions shall apply:

(a) "Cause" shall mean: (i) the Executive's conviction of, or plea of guilty or nolo contendere to, any felony (other than traffic-related offenses), (ii) the willful misconduct or gross negligence of the Executive with regard to the Company that the Board determines in good faith is, or is reasonably likely to be, materially injurious to the Company and its reputation, (iii) any incurable material breach by the Executive of this Agreement or the Invention Agreement or the Non-Competition Agreement (as such agreements are defined below), or (iv) the Executive's violation of the Company's published policies prohibiting unlawful harassment and discrimination or its published policy concerning drugs and alcohol, as in effect from time to time.

(b) "Change in Control" shall mean any of the following events provided that such event constitutes a "change in control event" within the meaning of Treasury Regulation 1.409A-3(i)(5)(i): the consummation of a merger, consolidation, reorganization, recapitalization or statutory share exchange involving the Company or a sale or other disposition of all or substantially all of the assets of the Company (a "Business Combination"), unless, immediately following such Business Combination all or substantially all of the individuals and entities who were the beneficial owners of the then-outstanding securities of the Company entitled to vote generally in the election of directors immediately prior to such Business Combination beneficially own, directly or indirectly, more than 50% of the combined voting power of the then-outstanding securities entitled to vote generally in the election of directors, respectively, of the resulting or acquiring corporation in such Business Combination (which shall include, without limitation, a corporation which as a result of such transaction owns the Company or substantially all of the Company's assets either directly or through one or more subsidiaries) in substantially the same proportions as their ownership of the then-outstanding securities of the Company entitled to vote generally in the election of directors immediately prior to such Business Combination.

(c) "Disability" shall mean any long-term disability or incapacity due to physical or mental illness that renders the Executive unable to substantially perform his duties for 90 consecutive days or 120 total days during any twelve (12) month period, provided that it may occur in a shorter period if, after its commencement, it is determined to be total and permanent by a physician selected by the Company and its insurers and such determination is acceptable to the Executive or to the Executive's legal representative (with such agreement on acceptability not to be unreasonably withheld).

(d) "Good Reason" shall mean the occurrence of any of the following events without Executive's prior written consent:

(i) a material diminution in the Executive's base compensation;

(ii) a material diminution in the Executive's then authority, duties or responsibilities;

(iii) a change in geographic location at which the Executive principally performs services of a distance of more than 50 miles (it being agreed for purposes of this clause the geographic locations at which the Executive principally performs services shall be both the location of his home and New Haven, Connecticut); provided, however, a move of the Company's principal corporate offices to Boston, Massachusetts or within 50 miles of Boston, Massachusetts, shall not constitute a change in geographic location for purposes of "Good Reason" under this Section 6(d)(iii).

(iv) any material breach by the Company of this Agreement;

provided, however, that no such event or condition shall constitute Good Reason unless (x) the Executive gives the Company a written notice of termination for Good Reason not more than 60 days after the initial existence of the condition, (y) the grounds for termination (if susceptible to correction) are not corrected by the Company within 30 days of its receipt of such notice and (z) the Executive's termination of employment occurs within 60 days following the Company's receipt of such notice.

7. **OTHER AGREEMENTS**. As a condition of the Executive's continued employment with the Company, the Executive hereby confirms his obligations under the Invention and Non-Disclosure Agreement (the "Invention Agreement"), dated March 1, 2011 with the Company, and that, concurrently with the execution of this Agreement, he shall execute the Non-Competition and Non-Solicitation Agreement (the "Non-Competition Agreement") attached hereto as Exhibit A and the Amendment Agreement to the Restricted Stock Agreement attached hereto as Exhibit B.

8. **INDEMNIFICATION AND INSURANCE**. The Executive shall be entitled to indemnification to the fullest extent permitted by the Company's Certificate of Incorporation and shall be entitled to coverage under the Company's directors' and officers' liability insurance policy to the same extent as other senior executives of the Company.

9. **NOTICE**. Any purported termination of employment hereunder shall be communicated through written notice from the terminating party. Such notice and all other communications that are required or may be given pursuant to the terms of this Agreement shall be in writing and shall be sufficient in all respects if given in writing and shall be deemed given: (i) if delivered personally, on the date of delivery; (ii) if mailed by certified or registered mail (return receipt requested and postage prepaid), three (3) days after the mailing date; (iii) if sent via a nationally recognized overnight courier, on the next business day thereafter; or (iv) if sent via facsimile confirmed in writing to the recipient, on the next business day thereafter. In each of the above cases, notice to the Company should be sent to the Company's principal place of business, notice to the Executive should be sent to his home address most recently on file with the Company, or notice to either the Company or the Executive should be sent to such other address or addresses as either party shall have designated in writing to the other party hereto.

10. **REPRESENTATION**. The Executive represents and warrants to the Company that he has the legal right to enter into this Agreement and to perform all of the obligations on his part to be performed hereunder in accordance with its terms and that he is not a party to any agreement or understanding, written or oral, which could prevent his from entering into this Agreement or performing all of his obligations hereunder.

11. **409A CONSIDERATIONS**.

(a) Subject to this Section 11, any severance payments or benefits that may be due under this Agreement shall begin only upon the date of the Executive's "separation from service" (determined as set forth below) which occurs on or after the termination of Executive's employment. The following rules shall apply with respect to distribution of the severance payments or benefits, if any, to be provided to the Executive under this Agreement, as applicable:

(i) It is intended that each installment of the severance payments or benefits under this Agreement provided under shall be treated as a separate "payment" for purposes of Section 409A of the Internal Revenue Code and the guidance issued thereunder ("Section 409A"). Neither the Company nor the Executive shall have the right to accelerate or defer the delivery of any such payments except to the extent specifically permitted or required by Section 409A.

(ii) If, as of the date of the Executive's "separation from service" from the Company, the Executive is not a "specified employee" (within the meaning of Section 409A), then each installment of the severance payments or benefits shall be made on the dates and terms set forth in this Agreement.

(iii) If, as of the date of the Executive's "separation from service" from the Company, the Executive is a "specified employee" (within the meaning of Section 409A), then:

(A) Each installment of the severance payments or benefits due under this Agreement that, in accordance with the dates and terms set forth herein, will in all circumstances, regardless of when the Executive's separation from service occurs, be paid within the short-term deferral period (as defined under Section 409A) shall be treated as a short-term deferral within the meaning of Treasury Regulation Section 1.409A-1(b)(4) to the maximum extent permissible under Section 409A and shall be paid on the dates and terms set forth in this Agreement; and

(B) Each installment of the severance payments or benefits due under this Agreement that is not described in this Section 11(a)(iii) and that would, absent this subsection, be paid within the six-month period following the Executive's "separation from service" from the Company shall not be paid until the date that is six months and one day after such separation from service (or, if earlier, the Executive's death), with any such installments that are required to be delayed being accumulated during the six-month period and paid in a lump sum on the date that is six months and one day following the Executive's separation from service and any subsequent installments, if any, being paid in accordance with the dates and terms set forth herein; provided, however, that the preceding provisions of this sentence shall not apply to any installment of payments if and to the maximum extent that that such installment is deemed to be paid under a separation pay plan that does not provide for a deferral of compensation by reason of the application of Treasury Regulation 1.409A-1(b)(9)(iii) (relating to separation pay upon an involuntary separation from service). Any installments that qualify for the exception under Treasury Regulation Section 1.409A-1(b)(9)(iii) must be paid no later than the last day of the Executive's second taxable year following the taxable year in which the separation from service occurs.

(b) The determination of whether and when the Executive's separation from service from the Company has occurred shall be made and in a manner consistent with, and based on the presumptions set forth in, Treasury Regulation Section 1.409A-1(h). Solely for purposes of this Section 11(b), "Company" shall include all persons with whom the Company would be considered a single employer under Section 414(b) and 414(c) of the Internal Revenue Code.

(c) All reimbursements and in-kind benefits provided under this Agreement shall be made or provided in accordance with the requirements of Section 409A to the extent that such reimbursements or in-kind benefits are subject to Section 409A, including, where applicable, the requirements that (i) any reimbursement is for expenses incurred during the Executive's lifetime (or during a shorter period of time specified in this Agreement), (ii) the amount of expenses eligible for reimbursement during a calendar year may not affect the expenses eligible for reimbursement in any other calendar year, (iii) the reimbursement of an eligible expense will be made on or before the last day of the calendar year following the year in which the expense is incurred and (iv) the right to reimbursement is not subject to set off or liquidation or exchange for any other benefit.

(d) The Company makes no representation or warranty and shall have no liability to the Executive or to any other person if any of the provisions of this Agreement (including this Section 11) are determined to constitute deferred compensation subject to Section 409A but that do not satisfy an exemption from, or the conditions of, that section.

12. **MISCELLANEOUS**. This Agreement sets forth the terms of the Executive's employment with the Company and supersedes any prior representations or agreements, whether written or oral, relating to the subject matter of this Agreement. This Agreement may be modified or amended only by an instrument in writing signed by the Executive and the Company. The Executive states and represents that he has had an opportunity to fully discuss and review the terms of this Agreement with an attorney. The Executive further states and represents that he has carefully read this Agreement, understands the contents herein, freely and voluntarily assents to all of the terms and conditions hereof, and signs his name of his own free act. This Agreement shall be governed by and construed in accordance with the internal laws of the State of New York, without regard to the conflict of law provisions thereof. This Agreement shall be binding upon, and inure to the benefit of, the Executive and the Company and the Executive's and the Company's respective heirs, successors, legal representatives and assigns. If any part of this Agreement is held by a court of competent jurisdiction to be invalid, illegible or incapable of being enforced in whole or in part by reason of any rule of law or public policy, such part shall be deemed to be severed from the remainder of this Agreement for the purpose only of the particular legal proceedings in question and all other covenants and provisions of this Agreement shall in every other respect continue in full force and effect and no covenant or provision shall be deemed dependent upon any other covenant or provision. This Agreement may be signed in one or more counterparts, each of which shall be deemed to be an original, but all of which together will constitute one and the same agreement. Facsimile copies of signed signature pages shall be binding originals.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the parties hereto have executed this Employment Agreement as of the date first written above.

TREVI THERAPEUTICS, INC.

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

THOMAS R. SCIASCIA

/s/ Thomas R. Sciascia

Exhibit A

Non-Competition and Non-Solicitation Agreement

NON-COMPETITION AND NON-SOLICITATION AGREEMENT

This Agreement is made between Trevi Therapeutics, Inc., a Delaware corporation (hereinafter referred to collectively with its subsidiaries as the "Company"), and Thomas R. Sciascia (the "Employee").

For good consideration and in consideration of the employment or continued employment of the Employee by the Company, the Employee and the Company agree as follows:

1. Non-Competition and Non-Solicitation. While the Employee is employed by the Company and for a period of two (2) years after the termination or cessation of such employment for any reason, the Employee will not directly or indirectly:

(a) Engage or assist others in engaging in any business or enterprise (whether as owner, partner, officer, director, employee, consultant, investor, lender or otherwise, except as the holder of not more than 1% of the outstanding stock of a publicly-held company) that develops, manufactures, markets, licenses, sells or provides any product intended for the treatment of pruritus or any other dermatological indication for which the Company has developed, manufactured, marketed, licensed, sold or provided a product, or planned to develop, manufacture, market, license, sell or provide a product, while the Employee was employed by the Company; or

(b) Either alone or in association with others, solicit, divert or take away, or attempt to divert or take away, the business or patronage of any of the clients, customers, or business partners of the Company which were contacted, solicited, or served by the Company during the 12-month period prior to the termination or cessation of the Employee's employment with the Company; or

(c) Either alone or in association with others (i) solicit, induce or attempt to induce, any employee or independent contractor of the Company to terminate his or her employment or other engagement with the Company, or (ii) hire, or recruit or attempt to hire, or engage or attempt to engage as an independent contractor, any person who was employed by the Company at any time during the term of the Employee's employment with the Company; provided, that this clause (ii) shall not apply to the recruitment or hiring or other engagement of any individual whose employment or other engagement with the Company has been terminated for a period of three months or longer.

(d) Extension. If the Employee violates the provisions of any of the preceding paragraphs of this Section 1, the Employee shall continue to be bound by the restrictions set forth in such paragraph until a period of one year has expired without any violation of such provisions.

2. Miscellaneous.

(a) Equitable Remedies. The restrictions contained in this Agreement are necessary for the protection of the business and goodwill of the Company and are considered by the Employee to be reasonable for such purpose. The Employee agrees that any breach of this Agreement is likely to cause the Company substantial and irrevocable damage which is difficult to measure. Therefore, in the event of any such breach or threatened breach, the Employee agrees that the Company, in addition to such other remedies which may be available, shall have the right to obtain an injunction from a court restraining such a breach or threatened breach and the right to specific performance of the provisions of this Agreement and the Employee hereby waives the adequacy of a remedy at law as a defense to such relief.

(b) Obligations to Third Parties. The Employee acknowledges and represents that this agreement and the Employee's employment with the Company will not violate any continuing obligation the Employee has to any former employer or other third party.

(c) Disclosure of this Agreement. The Employee hereby authorizes the Company to notify others, including but not limited to customers of the Company and any of the Employee's future employers or prospective business associates, of the terms and existence of this Agreement and the Employee's continuing obligations to the Company hereunder.

(d) Not Employment Contract. The Employee acknowledges that this Agreement does not constitute a contract of employment, does not imply that the Company will continue his/her employment for any period of time and does not change the at-will nature of his/her employment.

(e) Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of both parties and their respective successors and assigns, including any corporation with which, or into which, the Company may be merged or which may succeed to the Company's assets or business, provided, however, that the obligations of the Employee are personal and shall not be assigned by him or her. The Employee expressly consents to be bound by the provisions of this Agreement for the benefit of the Company or any subsidiary or affiliate thereof to whose employ the Employee may be transferred without the necessity that this Agreement be re-signed at the time of such transfer. Notwithstanding the foregoing, if the Company is merged with or into a third party which is engaged in multiple lines of business, or if a third party engaged in multiple lines of business succeeds to the Company's assets or business, then for purposes of Section 1(a), the term "Company" shall mean and refer to the business of the Company as it existed immediately prior to such event and as it subsequently develops and not to the third party's other businesses.

(f) Interpretation. If any restriction set forth in Section 1 is found by any court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it shall be interpreted to extend only over the maximum period of time, range of activities or geographic area as to which it may be enforceable.

(g) Severability. In case any provision of this Agreement shall be invalid, illegal or otherwise unenforceable, the validity, legality and enforceability of the remaining provisions shall in no way be affected or impaired thereby.

(h) Waivers. No delay or omission by the Company in exercising any right under this Agreement will operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion is effective only in that instance and will not be construed as a bar to or waiver of any right on any other occasion.

(i) Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York (without reference to the conflicts of laws provisions thereof). Any action, suit, or other legal proceeding which is commenced to resolve any matter arising under or relating to any provision of this Agreement shall be commenced only in a court of the State of New York (or, if appropriate, a federal court located within New York), and the Company and the Employee each consents to the jurisdiction of such a court. The Company and the Employee each hereby irrevocably waive any right to a trial by jury in any action, suit or other legal proceeding arising under or relating to any provision of this Agreement.

(j) Entire Agreement; Amendment. This Agreement supersedes all prior agreements, written or oral, between the Employee and the Company relating to the subject matter of this Agreement. This Agreement may not be modified, changed or discharged in whole or in part, except by an agreement in writing signed by the Employee and the Company. The Employee agrees that any change or changes in his/her duties, salary or compensation after the signing of this Agreement shall not affect the validity or scope of this Agreement.

(k) Captions. The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement.

[Remainder of Page Intentionally Left Blank]

THE EMPLOYEE ACKNOWLEDGES THAT HE/SHE HAS CAREFULLY READ THIS AGREEMENT AND UNDERSTANDS AND AGREES TO ALL OF THE PROVISIONS IN THIS AGREEMENT.

TREVI THERAPEUTICS, INC.

Date: _____

By: _____
President and Chief Executive Officer
Jennifer L. Good

Date: _____

THOMAS R. SCIASCIA

(Signature) _____

Exhibit B

Amendment Agreement to the Restricted Stock Agreement

TREVI THERAPEUTICS, INC.

Amendment Agreement to Restricted Stock Agreement

This Amendment Agreement to Restricted Stock Agreement (this "Amendment Agreement") is entered into by and between Trevi Therapeutics, Inc., a Delaware corporation (the "Company"), and Thomas R. Sciascia (the "Stockholder") as of the day of December, 2012.

WHEREAS, the Company has proposed to enter into on the date hereof a Series A Preferred Stock Purchase Agreement (the "Stock Purchase Agreement") with the investors listed on Exhibit A thereto (the "Investors") pursuant to which the Company will issue to such Investors shares of the Company's Series A Preferred Stock, $0.001 par value per share (the "Series A Financing");

WHEREAS, in order to induce the Investors to enter into the Stock Purchase Agreement and consummate the Series A Financing, the Stockholder has agreed to amend the vesting terms of the Restricted Stock Agreement, dated March 18, 2011 to which the Stockholder is a party with the Company (the "RSA");

NOW, THEREFORE, in consideration of the mutual promises and obligations contained herein and acting pursuant to Section 12(h) of the RSA, the Company and Stockholder do hereby consent and agree as follows:

1. Section 2. Section 2 of the RSA is hereby amended and restated in its entirety as follows:

"2. Purchase Option.

(a) In the event that the Stockholder ceases to be an Eligible Participant (as defined below) for any reason or no reason, with or without cause, prior to December , 2015, the Company shall have the right and option (the "Purchase Option") to purchase from the Stockholder, for a sum of $0.001 per share (the "Option Price"), some or all of the Unvested Shares (as defined below).

"Unvested Shares" means the total number of Shares multiplied by the Applicable Percentage at the time the Purchase Option becomes exercisable by the Company. The "Applicable Percentage" shall be (i) 50% less 1.3888% for each one-month period from and after December , 2012 during which the Stockholder is an Eligible Participant, and (ii) zero on or after December , 2015.

(b) Notwithstanding the foregoing, upon a Change in Control of the Company prior to December , 2015, 100% of the Shares shall become automatically vested in full and the Applicable Percentage shall be zero. For this purpose, a "Change in Control of the Company" shall mean the consummation of a merger, consolidation, reorganization, recapitalization or statutory share exchange involving the Company or a sale or other disposition of all or substantially all of the assets of the Company (a "Business Combination"), unless, immediately following such Business Combination all or substantially all of the individuals and entities who were the beneficial owners of the then-outstanding securities of the Company entitled to vote generally in the election of directors immediately prior to such Business Combination beneficially own, directly or indirectly, more than 50% of the combined voting power of the then-outstanding securities entitled to vote generally in the election of directors, respectively, of the resulting or acquiring corporation in such Business Combination (which shall include, without limitation, a corporation which as a result of such transaction owns the Company or substantially all of the Company's assets either directly or through one or more subsidiaries) in substantially the same proportions as their ownership of the then-outstanding securities of the Company entitled to vote generally in the election of directors immediately prior to such Business Combination.

(c) For purposes of this Agreement, the Stockholder shall be an "Eligible Participant" for so long as the Stockholder serves as an employee or officer of, or consultant or advisor to, the Company or a parent or subsidiary of the Company."

2. Miscellaneous.

(a) Each capitalized term used and not otherwise described herein shall have the meaning ascribed to such term in the RSA.

(b) Except as expressly provided herein, all provisions of the RSA shall remain in full force and effect.

(c) This Amendment Agreement shall be governed by and construed and interpreted in accordance with the laws of the State of Delaware, without regard to its rules pertaining to conflicts of laws thereunder.

(d) This Amendment Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[The remainder of this page is intentionally left blank.]

IN WITNESS WHEREOF, the parties hereto have executed this Amendment Agreement as of the date first written above.

COMPANY:

TREVI THERAPEUTICS, INC.

By: _____
Name: Jennifer L. Good
Title: President and Chief Executive Officer

STOCKHOLDER:

_____
Thomas R. Sciascia

[Signature Page to Amendment Agreement]

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-231260) pertaining to the 2012 Stock Incentive Plan, as amended, the 2019 Stock Incentive Plan, and the 2019 Employee Stock Purchase Plan of Trevi Therapeutics, Inc. of our report dated March 16, 2020, with respect to the consolidated financial statements of Trevi Therapeutics, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Stamford, Connecticut

March 16, 2020

Exhibit 31.1

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

I, Jennifer L. Good, certify that:

1. I have reviewed this Annual Report on Form 10-K 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: March 16, 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 Annual Report on Form 10-K 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: March 16, 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 Annual Report on Form 10-K of Trevi Therapeutics, Inc. (the "Company") for the period ended December 31, 2019, 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: March 16, 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 Annual Report on Form 10-K of Trevi Therapeutics, Inc. (the "Company") for the period ended December 31, 2019, 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: March 16, 2020

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