# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, D.C. 20549**

## FORM 10-K

☒ **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**

**COMMISSION FILE NUMBER: 001-36279**

# CARA THERAPEUTICS, INC.
**(Exact name of registrant as specified in its charter)**

| **Delaware** | **75-3175693** |
|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(I.R.S. Employer Identification No.)** |
| **4 Stamford Plaza<br>107 Elm Street, 9th Floor<br>Stamford, Connecticut** | **06902** |
| **(Address of registrant's principal executive offices)** | **(Zip Code)** |

**Registrant's telephone number, including area code: (203) 406-3700**

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

| Title of each class | Trading Symbol | Name of each exchange on which registered |
|---|---|---|
| Common Stock, par value $0.001 per share | CARA | 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 Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 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 | ☐ |
| | | Smaller Reporting Company | ☐ |
| Non-accelerated filer | ☐ | 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 Act). Yes ☐ No ☒

The aggregate market value of the registrant's Common Stock (the only common equity of the registrant) held by non-affiliates, based on the closing sales price of the stock on the Nasdaq Global Market for the last business day of the registrant's most recently completed second fiscal quarter, was $783,719,032. For purposes of this calculation, shares of common stock held by directors and officers and their affiliated entities at June 30, 2019 were excluded. Exclusion of shares held by any person should not be construed to indicate that the person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant, or that the person is controlled by or under common control with the registrant.

The number of shares outstanding of the registrant's Common Stock, par value $0.001 per share, as of February 24, 2020 was 46,725,225.

**Documents Incorporated By Reference**

Portions of the registrant's Proxy Statement for its 2020 Annual Meeting of Stockholders, to be filed with the Securities and Exchange Commission no later than 120 days after December 31, 2019, are incorporated by reference in Part III of this Annual Report on Form 10-K.

**CARA THERAPEUTICS, INC.**
**2019 ANNUAL REPORT ON FORM 10-K**

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## PART I

*In this Annual Report on Form 10-K, the terms "we," "us" and "our" refer to Cara Therapeutics, Inc.*

### Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that involve substantial risks and uncertainties. The forward-looking statements are contained principally in the sections of this Annual Report on Form 10-K titled "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business," but are also contained elsewhere in this Annual Report on Form 10-K. In some cases, you can identify forward-looking statements by the words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," "will," or "would," and or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain.

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

- the success and timing of our clinical trials and reporting of our results from these trials, including our clinical trial programs for KORSUVA™ (CR845/difelikefalin) injection in chronic kidney disease associated pruritus, or CKD-aP, and for Oral KORSUVA (CR845/difelikefalin) in CKD-aP, chronic liver disease associated pruritus, or CLD-aP, and pruritus associated with atopic dermatitis, or AD;
- our plans to develop and commercialize KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) and any future product candidates;
- the potential results of ongoing and planned preclinical studies and clinical trials and future regulatory and development milestones for our product candidates;
- the size and growth of the potential markets for pruritus management, including CKD-aP in hemodialysis and non-dialysis markets, CLD-aP and AD markets as well as post-operative care markets;
- the potential regulatory development pathway for KORSUVA (CR845/difelikefalin) injection in CKD-aP and CR845/difelikefalin injection in acute post-operative setting;
- the rate and degree of market acceptance of any approved products;
- our ability to obtain and maintain regulatory approval of our product candidates, and the labeling under any approval we may obtain;
- the anticipated commercial launch of our lead product candidate, KORSUVA (CR845/difelikefalin) injection;
- the anticipated use of Enteris's Peptelligence® technology to develop, manufacture and commercialize Oral KORSUVA (CR845/difelikefalin);
- the potential of future scheduling of KORSUVA (CR845/difelikefalin) injection by the United States Drug Enforcement Administration, or DEA, if regulatory approval is received;

- the performance of our current and future collaborators and licensees, including Vifor Fresenius Medical Care Renal Pharma Ltd., or VFMCRP, Maruishi Pharmaceuticals Co. Ltd., or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or CKDP, as well as sub-licensees, including Kissei Pharmaceutical Co. Ltd., or Kissei, and our ability to maintain such collaborations;
- our ability to establish additional collaborations for our product candidates;
- the continued service of our key scientific or management personnel;
- our ability to establish commercialization and marketing capabilities;
- regulatory developments in the United States and foreign countries;
- our ability to obtain and maintain coverage and adequate reimbursement from third-party payers for any approved products;
- our planned use of our cash and cash equivalents and marketable securities and the clinical milestones we expect to fund with such proceeds;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- our ability to obtain funding for our operations;
- our ability to obtain and maintain intellectual property protection for our product candidates and our ability to operate our business without infringing on the intellectual property rights of others;
- the success of competing drugs that are or may become available; and
- the performance of third-party manufacturers and clinical research organizations, or CROs.

You should refer to Part I Item 1A. “Risk Factors” of this Annual Report on Form 10-K for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report on Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K and have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

**Industry and Market Data**

We obtained the industry and market data in this Annual Report on Form 10-K from our own research as well as from industry and general publications, surveys and studies conducted by third parties. Industry and general publications, studies and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. These third parties may, in the future, alter the manner in which they conduct surveys and studies regarding the markets in which we operate our business. As a result, you should carefully consider the inherent risks and uncertainties associated with the industry and market data contained in this Annual Report on Form 10-K, including those discussed in Part I Item 1A. “Risk Factors.”

**Item 1. *Business*.**

**Overview**

We are a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors, or KORs. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), a first-in-class KOR agonist that targets KORs located in the peripheral nervous system and on immune cells.

In our KALM™-1 Phase 3 trial and two Phase 2 trials, KORSUVA (CR845/difelikefalin) injection (intravenous formulation) has demonstrated statistically significant reductions in itch intensity and concomitant improvement in pruritus-related quality of life measures in hemodialysis patients with moderate-to-severe CKD-aP. We are continuing to investigate KORSUVA (CR845/difelikefalin) injection in our global KALM-2 Phase 3 trial in hemodialysis patients with moderate-to-severe CKD-aP. We have partnered with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, to commercialize KORSUVA (CR845/difelikefalin) injection in dialysis patients with CKD-aP worldwide, excluding the United States, Japan (Maruishi/sub-licensee Kissei), and South Korea (CKDP). We retain all rights in the United States and will promote KORSUVA (CR845/difelikefalin) injection, if approved, with VFMCRP in U.S. Fresenius Medical Care North America, or FMCNA, dialysis clinics under a profit share agreement.

CR845/difelikefalin has also demonstrated statistically significant pain reduction in clinical trials in patients with moderate-to-severe acute pain in the post-operative setting, without inducing many of the undesirable side effects typically associated with currently available opioid pain therapeutics. We retain rights to all KORSUVA/CR845 formulations and indications worldwide, excluding KORSUVA (CR845/difelikefalin) injection in dialysis patients with CKD-aP under our agreement with VFMCRP for certain ex-U.S. territories and our other license agreements for CR845/difelikefalin in Japan (Maruishi/sub-licensee Kissei) and South Korea (CKDP).

The U.S. Food and Drug Administration, or FDA, has conditionally accepted KORSUVA as the trade name for CR845/difelikefalin injection and its safety and efficacy have not been fully evaluated by any regulatory authority.

We were incorporated and commenced operations in 2004, and our primary activities to date have been organizing and staffing our company, developing our product candidates, including conducting preclinical studies and clinical trials of CR845/difelikefalin-based product candidates and raising capital. To date, we have financed our operations primarily through sales of our equity and debt securities and payments from license agreements. We have no products currently available for sale, and substantially all of our revenue to date has been revenue from license agreements, although we have received nominal amounts of revenue under research grants and the sale of clinical compound.

**Recent Developments**

*Departure of Executive Officer*

Dr. Mani Mohindru, our former Chief Financial Officer and Chief Strategy Officer, resigned from our company effective as of December 20, 2019 to accept a new opportunity with a privately held company. We have commenced a search for Dr. Mohindru’s replacement.

*2019 Inducement Plan*

On October 30, 2019, our Board of Directors, or the Board, adopted the 2019 Inducement Plan, which is a non-stockholder approved stock plan adopted pursuant to the “inducement exception” provided under Nadsaq Listing Rule 5635(c)(4), or Rule 5635, for the purpose of awarding (i) non-statutory stock options, (ii) restricted stock awards, (iii) restricted stock unit awards, (iv) other stock awards to new employees as inducement material to such new employees entering into employment with us. On November 20, 2019, we filed a Registration Statement on Form S-8 with the U.S. Securities and Exchange Commission, or the SEC, covering the offering of up to 300,000 shares of our common stock, par value $0.001, pursuant to the 2019 Inducement Plan. We have granted 47,500 stock options under the 2019 Inducement Plan as of December 31, 2019.

*License Agreement with Enteris Biopharma, Inc.*

On August 20, 2019, we entered into a Non-Exclusive License Agreement, or the Enteris License Agreement, with Enteris Biopharma, Inc., or Enteris. Pursuant to the Enteris License Agreement, Enteris granted to us a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

In connection with the Enteris License Agreement, on August 20, 2019, we entered into a Stock Purchase Agreement, or the Purchase Agreement, with Enteris and its affiliate, EBP Holdco LLC, pursuant to which we issued and sold to Enteris and its affiliate 170,793 shares of our common stock in a private placement in satisfaction of a portion of the upfront fee payable pursuant to the Enteris License Agreement. Refer to "Item 1. *Business* – Manufacturing and Licensing Agreements" for further detail.

*Follow-on Public Offering*

On July 24, 2019, we entered into an underwriting agreement with J.P. Morgan Securities LLC and Jefferies LLC, as representatives of the several underwriters named therein, relating to the issuance and sale by us of up to 6,325,000 shares of our common stock, including 825,000 additional shares of common stock that the underwriters had the option to purchase, at a public offering price of $23.00 per share. We closed this offering on July 29, 2019, including the full exercise of the underwriters' option to purchase additional shares of common stock. We received net proceeds of $136.5 million, after deducting $9.0 million of underwriting discounts and commissions and offering expenses.

This offering was pursuant to our Registration Statement on Form S-3 (File No. 333-230333), or the Shelf Registration Statement, filed with the SEC on March 15, 2019 and declared effective on April 4, 2019, and a related prospectus supplement dated July 24, 2019, which was filed with the SEC on July 25, 2019. The Shelf Registration Statement provides for aggregate offerings of up to $300.0 million of common stock, preferred stock, debt securities, warrants or any combination thereof. The securities registered under this Shelf Registration Statement include unsold securities that had been registered under our previous Registration Statement on Form S-3 (File No. 333-216657) that was declared effective on March 24, 2017.

*Manufacturing Agreement with Patheon UK Limited*

On July 8, 2019, we entered into a Master Manufacturing Services Agreement, or MSA, with Patheon UK Limited, or Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to us for the drug products specified by us from time to time. Refer to "Item 1. *Business* – Manufacturing and Licensing Agreements" for further detail.

**The Market Opportunity – Pruritus**

Pruritus, or itch, is defined as an unpleasant sensation that provokes the desire to scratch. Certain systemic diseases have been known to cause pruritus that ranges in intensity from a mild annoyance to an intractable, disabling condition. Itch originates in the epidermis and dermal–epidermal junction and is transmitted by itch-selective sensory neuron C fibers, or pruriceptors. Some of these fibers are sensitive to histamine while others are not, and there is evidence for histamine-insensitive C fibers that are activated by numerous itch-inducing substances or pruritogens, many of which initiate signals through interaction with specific G-protein-coupled receptors. In addition, there is increasing evidence for the differential involvement of these systems in various forms of itch which may involve disease-specific pruritogens. As an example, chronic pruritus associated with kidney failure is thought to involve complex interactions among peripheral cells (T cells, mast cells, neutrophils, eosinophils, and keratinocytes) and histamine-insensitive nerve fibers, involving increased release of cytokines, proteases, and neuropeptides, interacting with multiple receptors that lead to exacerbation of itch. These different peripheral cell types express kappa opioid receptors, which can regulate the release of these pruritogenic substances, while the kappa opioid receptors on C fibers are thought to regulate their response to these pruritogens. Because kappa opioid receptors are expressed in peripheral tissues, there is a potential to modulate itch

signals peripherally without impacting the central kappa opioid receptors. The itch-sensitive sensory nerve fibers transmit signals to the cell bodies in the dorsal root ganglia (that also have kappa opioid receptors), which send fibers to enter the spinal cord. Itch signals then ascend via the spinothalamic tract to multiple brain areas for sensory processing and interactions with cognitive and other systems.

Additionally, the activation of kappa receptors via an agonist is thought to reduce itching by functionally counteracting increased mu opioid receptor activity which is suggested to be associated with some chronic forms of pruritus. Activation of the mu opioid receptor in the brain and in the peripheral nerve endings results in itching while non-selective mu opioid antagonists can inhibit itching. Kappa opioid receptor stimulation inhibits the effects of mu receptor activation both centrally and peripherally.

Pruritus may be classified into different categories on the basis of the underlying causative disease: renal or CKD-aP (previously known as uremic pruritus), cholestatic pruritus, dermatological pruritus, hematologic pruritus, endocrine pruritus, pruritus related to malignancy and idiopathic generalized pruritus. According to a study we conducted with IMS Health (now IQVIA) utilizing medical claims data from 2013, approximately 21 million patients received a prescription for an anti-pruritic agent such as corticosteroids, antihistamines, select antidepressants, counterirritants, bile acid sequestrants, rifampin, narcotic antagonists and partial agonists, topical immunomodulators or gabapentin.

***Chronic Kidney Disease-Associated Pruritus (CKD-aP)***

According to the National Kidney Foundation, or NKF, it is estimated that 37 million people (15% of the adult population) have chronic kidney disease, or CKD, in the United States alone, yet many of these patients remain undiagnosed. According to a study conducted by IQVIA, in 2017, approximately 7.3 million patients were diagnosed with CKD in the United States and roughly 33% or approximately 2.4 million patients received a prescription for an anti-pruritic. A separate epidemiological study published in 2019 in the Clinical Journal of American Society of Nephrology shows that approximately 25% of stage III to V (moderate-to-severe) CKD patients suffer from moderate-to-severe pruritus or itching.

CKD-aP (also known as uremic pruritus) can occur in patients with CKD as well as End Stage Renal Disease, or ESRD, and is commonly seen in patients receiving hemodialysis. According to Fresenius Medical Care, a world leading provider of products and medical care for dialysis patients, there were approximately 3.2 million patients globally undergoing dialysis in 2017. According to the Dialysis Outcomes and Practice Patterns Study published in December 2017 in the Clinical Journal of the American Society of Nephrologists, it is estimated that nearly 70% of these patients suffer from some form of CKD-aP with approximately 40% of these patients experiencing moderate to severe pruritus.

Currently, there are no approved products in the United States or Europe to treat CKD-aP. Patients are generally managed with a multitude of products including corticosteroids, gabapentin, antihistamines, antidepressants and others with varying degrees of success. There is one product, nalfurafine (Remitch®) marketed by Toray Industries, approved to treat CKD-aP in Japan only. It is not approved either in the United States or Europe for CKD-aP.

***Pruritus Associated with Atopic Dermatitis (AD)***

AD is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 5% of adults. Chronic pruritus is one of the defining features of AD. The itch is so common in AD that AD is often described as the itch that rashes. The point prevalence of chronic pruritus ranges between 87% to 100% in AD. Both quality of life and psychosocial well-being are known to negatively correlate with itch severity. The associated psychosocial morbidity of this distressing symptom includes sleep disruption, depression, agitation, anxiety, altered eating habits, reduced self-esteem and difficulty concentrating.

The cause of AD is multifactorial, including genetic predisposition, impaired skin barrier, environmental triggers and immune dysregulation. The sensation of itch in AD is similarly complex. Chronic itch in AD is mediated by a complex interplay between keratinocytes, cutaneous nerve fibers, pruritogenic molecules and the peripheral and central

nervous system. An imbalance in the epidermal opioid system has also been described as potentially playing a role in the modulation of pruritus in AD.

***Chronic Liver Disease-Associated Pruritus (CLD-aP)***

Millions of Americans suffer from chronic liver disease, or CLD, of various etiologies ranging from hepatitis to cirrhosis to primary biliary cholangitis, or PBC. Pruritus is a common and irritating symptom in patients who suffer from CLD, especially those with chronic cholestatic disease. Severe pruritus can have debilitating effects and can lead to a significant reduction in a patient's quality of life. According to a study conducted by IQVIA, nearly 7.0 million patients were diagnosed with CLD in 2013 in the United States and approximately 37% percent or 2.5 million patients received a prescription for an anti-pruritic.

There are no approved therapies for CLD-aP in the United States. Current antipruritic therapies, primarily antihistamines and corticosteroids as well as other therapies tried off-label, are largely ineffective in treating the disease and/or can produce significant side effects.

***Other Causes of Pruritus***

There are many other systemic diseases that can trigger pruritus in patients. They include endocrinologic disease (e.g. hyperthyroidism), malignancy (e.g. Hodgkin lymphoma), hematologic disease (e.g. polycythemia vera), psoriasis, hives/urticarial, and lice/scabies. Data from a Cara-sponsored IMS Health (now IQVIA) study, utilizing medical claims data from 2013, indicate that over 20 million prescriptions for anti-pruritic therapeutics are filled annually in the United States.

**The Market Opportunity – Post-Operative Nausea and Vomiting (PONV) Management**

PONV in a hospital or other medical setting in the United States is most often treated with 5-HT3 antagonists (e.g. ondansetron), NK-1 receptor antagonists (e.g. aprepitant) steroids (dexamethasone), dopamine receptor antagonists (haloperidol, metoclopramide) as well as Anticholinergics (scopolamine patch) either alone in low risk patients or in combination in patients with a higher risk of PONV. According to an article published in Best Practice & Research Clinical Anaesthesiology, PONV is one of the most important factors in determining length of stay after surgery, resulting in estimated annual costs in the United States in the range of $1 billion. Per IQVIA, in 2017, there were over 700 million units of PONV drugs sold in the United States.

The market for the prevention and treatment of PONV is highly fragmented. Anesthesiologists utilize a number of different agents alone or in combination (particularly in patients with a high risk for PONV) with different mechanism of actions to try to manage PONV. If approved, I.V. CR845/difelikefalin would likely be competing within the overall PONV market, although we expect that it would primarily be utilized as an add-on therapy in patients with a higher risk of PONV. Although most of the PONV products are generically available, there is still a significant segment of high-risk patients where their PONV is not adequately managed, which can increase the hospital length of stay and add significant cost to managing a post-operative patient.

**Our Strategy**

Our strategy is to develop and commercialize a novel and first-in-class portfolio of peripherally-acting kappa opioid receptor agonists, with KORSUVA (CR845/difelikefalin) injection and Oral KORSUVA (CR845/difelikefalin) as our lead candidates. We have designed and are developing product candidates which have clearly defined clinical development programs and target significant commercial market opportunities. The key elements of our strategy are as follows:

***Advance KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe CKD-aP in patients undergoing hemodialysis to support regulatory approval.*** In January 2018, based on positive data from our earlier Phase 2 studies, we initiated the first pivotal Phase 3 trial (KALM-1) of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients suffering from moderate to severe CKD-aP. In May 2019, we announced positive top-line results

from this trial. The study met the primary and all secondary efficacy endpoints. In August 2018, we initiated a global Phase 3 study (KALM-2) with KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP in multiple countries worldwide, including the United States. We expect top-line data from the global study to read out in the second quarter of 2020. In addition, we currently have a safety database in line with International Conference on Harmonization, or ICH, guidelines for NDA submission, with over 1,500 total patient exposures as well as sufficient patient numbers that completed six months and 12 months of treatment. These safety exposures will support filings for regulatory approval in the United States and other non-U.S. markets. In June 2017, the FDA granted Breakthrough Therapy Designation to KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in hemodialysis patients, for which there are currently no approved therapies in the United States. The Breakthrough Therapy Designation was in part supported by positive data from our previous Phase 2 efficacy studies.

***Build a specialty sales and marketing organization to commercialize KORSUVA (CR845/ difelikefalin) injection for the treatment of CKD-aP in hemodialysis patients in the United States, if approved.*** If KORSUVA (CR845/ difelikefalin) injection is approved by the FDA for the treatment of CKD-aP in hemodialysis patients, we expect to establish a sales force to market to nephrologists in dialysis centers across the United States. We also intend to build a supportive commercialization organization as well as establish a reimbursement strategy and infrastructure to support our sales and marketing efforts. We do not intend to commercialize KORSUVA (CR845/difelikefalin) injection for CKD-aP in hemodialysis patients on our own outside the United States. In May 2018, we licensed worldwide rights, excluding the United States, Japan and South Korea, to commercialize KORSUVA (CR845/difelikefalin) injection for the treatment CKD-aP in dialysis patients to VFMCRP, a joint venture of Vifor Pharma Group (SIX: VIFN) and Fresenius Medical Care (NYSE: FMS) that specializes in treatments for CKD. Under the agreement, VFMCRP has the exclusive rights to commercialize KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in dialysis patients in all countries outside the United States except in Japan and South Korea. We retain full development and commercialization rights for KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in the United States except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where we and VFMCRP will promote KORSUVA (CR845/difelikefalin) injection under a profit-sharing arrangement based on net FMCNA clinic sales recorded by Cara. In addition, we already have development and commercialization agreements with Maruishi and CKDP for development of CR845/difelikefalin for the Japanese and South Korean markets, respectively.

***Expand the use of Oral KORSUVA (CR845/difelikefalin) in other pruritic indications by establishing proof-of-concept in clinical conditions such as non-dialysis stage III-V CKD-aP, CLD-aP and AD.*** Based on potent anti-pruritic effect we observed with KORSUVA (CR845/difelikefalin) injection in CKD-aP in hemodialysis patients as well as the data we and others have generated in preclinical models of itch, we have initiated clinical programs with Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in patients with stage III to V (moderate-to-severe) CKD, in patients with CLD-aP, and patients with AD. In July 2018, we initiated a double blind, randomized, placebo-controlled Phase 2 study with Oral KORSUVA (CR845/difelikefalin) in stage III to V (moderate-to-severe) CKD patients with CKD-aP. In December 2019, we announced top-line data from this trial indicating that patients treated with the 1.0 mg tablet strength of Oral KORSUVA (CR845/difelikefalin) achieved the primary endpoint of statistically significant reduction in weekly mean of the daily worst itching NRS scores vs. placebo after the 12-week treatment period (-4.4 KORSUVA vs. -3.3 placebo, p=0.018). In mid-2019, we also initiated Phase 2 trials of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in patients with hepatic impairment due to PBC and in patients with AD. We aim to report top-line data from both of these trials in 2020.

***Establish partnerships for further development and commercialization of I.V. CR845/difelikefalin for the treatment of moderate-to-severe acute pain and/or PONV in acute care settings in the United States.*** In June 2018, we reported positive top-line data from the adaptive Phase 2/3 post-operative pain trial of I.V. CR845/ difelikefalin in patients undergoing abdominal surgeries. At the higher dose of 1.0 mcg/kg dose, I.V. CR845/ difelikefalin demonstrated statistically significant reductions in pain intensity compared to placebo at all pre-specified post-operative assessment periods. Additionally, I.V. CR845 treatment resulted in statistically significant reductions in the incidence of post-operative nausea and vomiting over the 24-hour period post-surgery for both the lower and higher doses of 0.5 and 1.0 mcg/kg, respectively. We are currently assessing the best path forward for I.V. CR845/difelikefalin in the post-operative acute care setting and have received FDA input regarding PONV as a potential indication. We expect to seek partnerships for further development of I.V. CR845/difelikefalin in the acute care setting.

**Our Product Candidates**

Our product candidate, CR845/difelikefalin, is a new chemical entity, which is designed to selectively stimulate kappa, rather than mu, and delta opioid receptors. CR845/difelikefalin has been designed with specific chemical characteristics to restrict its entry into the CNS and further limit its mechanism of action to KORs in the peripheral nervous system and on immune cells. Activation of kappa receptors in the CNS is known to result in some undesirable effects, including dysphoria. Since CR845/difelikefalin modulates kappa receptor signals peripherally without any significant activation of opioid receptors in the CNS, it is generally not expected to produce the CNS-related side effects of mu opioid agonists (such as addiction and respiratory depression) or centrally-active kappa opioid agonists (such as dysphoria and hallucinations). CR845/difelikefalin has been administered to more than 3,000 human subjects in Phase 1, Phase 2 and Phase 3 clinical trials as an I.V. infusion, bolus intravenous injection or oral capsule or tablet, and thus far has been observed to be generally well tolerated in multiple clinical trials.

Based on the non-clinical and clinical studies we have completed to date, we believe that CR845/difelikefalin, if approved, would be attractive to both patients and physicians as a treatment for moderate-to-severe pruritus associated with certain diseases such as CKD, CLD and dermatological conditions such as AD as well as moderate-to-severe pain due to the following attributes:

- novel, peripherally-acting, KOR agonist mechanism of action;
- evidence of efficacy in completed clinical trials of pruritus and pain;
- potential for reducing mu opioid use and opioid-related adverse events, or AEs, such as nausea and vomiting;
- potential for reduction of post-operative nausea and vomiting, or PONV;
- avoidance of mu opioid-related CNS side effects, such as respiratory depression and euphoria;
- lower potential for addiction or abuse liability;
- avoidance of interactions with other drugs because CR845/difelikefalin is not metabolized in the liver and does not interact with liver enzymes responsible for the metabolism of most commonly used classes of drugs; and
- availability in injectable form for the treatment of pruritus in CKD patients undergoing hemodialysis in the hospital and dialysis center settings as well as for pain and/or PONV treatment in the acute care setting and oral form for treatment of pruritus or chronic pain conditions in the outpatient setting.

Our current product candidate pipeline is summarized in the table below:

| Program | Product Candidate | Primary Indication | Status | Commercialization Rights |
|---|---|---|---|---|
| **Pruritus** | KORSUVA (CR845/ difelikefalin) Injection | Pruritus CKD – Hemodialysis | KALM-2 (Global) Phase 3 efficacy trials ongoing; interim assessment complete – target enrollment increased to 430 patients<br>KALM-1: double blind phase completed; top-line data reported<br>Phase 3 safety trials ongoing<br>Breakthrough Therapy Designation granted by FDA in June 2017 | Cara (United States); Maruishi (Japan); CKDP (South Korea); VFMCRP (Worldwide, other than the United States, Japan and South Korea) |
| | Oral KORSUVA (CR845/difelikefalin) | Pruritus CKD (Stage III - V) | Phase 2 trial completed; top-line data reported | Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea) |
| | Oral KORSUVA (CR845/difelikefalin) | Pruritus CLD – PBC | Phase 2 efficacy trial ongoing | Cara (Worldwide, other than South Korea); CKDP (South Korea) |
| | Oral KORSUVA (CR845/difelikefalin) | Pruritus AD | Phase 2 efficacy trial ongoing | Cara (Worldwide, other than South Korea); CKDP (South Korea) |
| **Post-Op Setting** | CR845/difelikefalin Injection | Acute Post-Operative Pain/PONV | Adaptive Phase 2/3 trial completed; top-line data reported | Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea) |

***KORSUVA (CR845/Difelikefalin) Injection for Treatment of Chronic Kidney Disease-Associated Pruritus (CKD-aP)***

CKD-aP is an intractable systemic itch condition with high prevalence for which there are no approved therapeutics in the United States or Europe.

In May 2019, we announced positive results from the double blinded phase of the first pivotal Phase 3 efficacy trial (KALM-1) of KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in patients undergoing hemodialysis. The trial met the primary and all secondary endpoints after 12 weeks of treatment. This trial was initiated in the first quarter of 2018 in the United States and has entered into the 52-week open label extension phase. In August 2018, we initiated the second pivotal Phase 3 efficacy trial, KALM-2 (with a 52-week open label extension phase) of KORSUVA (CR845/difelikefalin) injection that enrolled patients in the United States and multiple countries outside the United States. In October 2019, we completed an interim statistical assessment of KALM-2 and based on the recommendation of the Independent Data Monitoring Committee, or IDMC, the size of the trial was increased from the original enrollment target of 350 patients to a new target of 430 patients. The KALM-2 trial was fully enrolled in December 2019 and we expect to report top-line data in the second quarter of 2020. In addition to these trials, we are also conducting 52-week and 12-week Phase 3 open label safety studies of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP. Based on the current status of our completed and ongoing efficacy and safety trials, we expect to file the NDA for KORSUVA (CR845/difelikefalin) injection in the second half of 2020.

In June 2017, the FDA granted breakthrough therapy designation for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe pruritus in patients with CKD undergoing hemodialysis. This regulatory decision was supported by positive results from Phase 2 clinical trials of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP. Breakthrough therapy designation is granted to expedite the development and review process for new therapies addressing serious or life-threatening conditions, where preliminary clinical evidence indicates that the drug candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

*KALM-1 and KALM-2 Phase 3 Efficacy Trials of KORSUVA (CR845/Difelikefalin) Injection*

In January 2018, we initiated the first Phase 3 efficacy trial (KALM-1) to support regulatory filings for the approval of KORSUVA (CR845/difelikefalin) injection. This U.S. study is a multicenter, randomized, double-blind, placebo-controlled 12-week treatment trial (with a 52-week open label extension phase) that is designed to evaluate the safety and efficacy of 0.5 mcg/kg of KORSUVA (CR845/difelikefalin) injection to be administered three times per week after dialysis in 350 hemodialysis patients with moderate-to-severe pruritus (with a pre-specified interim assessment that allowed for expansion of the study to up to 500 patients, if needed).

In May 2019, we announced positive top-line results from this trial. The study met the primary efficacy endpoint with 51% of the patients receiving 0.5 mcg/ kg of KORSUVA (CR845/difelikefalin) injection versus 28% of patients receiving placebo achieving at least a 3-point improvement from baseline with respect to the weekly mean of the daily 24-hour worst itching intensity numeric rating scale, or NRS, score at week 12 (p= 0.000019). The study also met all secondary endpoints, including assessment of itch-related quality of life changes measured using self-assessment Skindex-10 (patients receiving KORSUVA experienced 43% improvement versus patients receiving placebo, p= 0.0004) and 5-D Itch scales (patients receiving KORSUVA experienced 35% improvement versus patients receiving placebo, p= 0.0009). In addition, 39% of patients receiving KORSUVA (CR845/difelikefalin) injection achieved a four-point or greater improvement from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 12 versus 18% for patients receiving placebo (p= 0.000032), another key secondary endpoint. In this trial, KORSUVA (CR845/difelikefalin) injection was generally well-tolerated with a safety profile consistent with that seen in earlier trials. Overall, the incidence of adverse effects, or AEs, and serious AEs were similar across both KORSUVA (CR845/difelikefalin) injection and placebo groups. The most common treatment emergent AEs reported in greater than 5% of patients were diarrhea (9.5% KORSUVA vs 3.7% placebo), dizziness (6.9% KORSUVA vs 1.1% placebo), vomiting (5.3% KORSUVA vs 3.2% placebo) and nasopharyngitis (3.2% KORSUVA vs 5.3% placebo).

In August 2018, we announced the dosing of the first patient in the second Phase 3 efficacy trial (KALM-2) that is similar in design and size to the KALM-1 Phase 3 trial (with a pre-specified interim assessment that allows for expansion of the study to up to 500 patients, if needed) and will facilitate regulatory filings worldwide. This second Phase 3 trial enrolled hemodialysis patients with moderate-to-severe pruritus in the United States as well as in multiple countries in Europe and Asia Pacific. In October 2019, we completed an interim statistical assessment of KALM-2 and based on the recommendation of the IDMC, the target size of the trial has been increased to 430 patients versus the original enrollment target of 350 patients. The IDMC's recommendation was based on the results of a prespecified interim conditional power assessment that was conducted after approximately 50% of the originally targeted patients completed the designated 12-week treatment period. The KALM-2 trial was fully enrolled in December 2019, and we expect to report top-line data in the second quarter of 2020.

*Phase 3 Safety Trials of KORSUVA (CR845/Difelikefalin) Injection*

In the second quarter of 2017, we initiated a 52-week Phase 3 safety trial that was expected to enroll up to 300 hemodialysis patients with CKD-aP, including those who have completed prior Phase 2 trials of KORSUVA (CR845/difelikefalin) injection as well as patients who have not been previously exposed to CR845/difelikefalin. This open-label trial is evaluating the long-term safety of KORSUVA (CR845/difelikefalin) injection at the dose of 0.5mcg/kg. The study is now fully enrolled at 288 patients.

In the second quarter of 2019, we initiated an additional open label Phase 3 safety trial of KORSUVA (CR845/difelikefalin) injection that is expected to enroll up to 250 hemodialysis patients with CKD-aP. This trial is designed to evaluate primarily safety as well as effectiveness of 0.5 mcg/kg dose of KORSUVA (CR845/difelikefalin) injection for up to 12 weeks treatment in hemodialysis patients with CKD-aP.

Currently, more than 1,500 total patient exposures have been achieved, including all ongoing safety trials, with more than 600 patients completing at least six months of treatment and more than 300 patients completing one year of treatment.

The design and dose selection for our Phase 3 trials are based on results of the previously completed Phase 2 trials of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP in consultation with the FDA as part of our End of Phase 2 meeting with the FDA that was held in 2017.

***Oral KORSUVA (CR845/Difelikefalin) for Treatment of Chronic Kidney Disease-Associated Pruritus (CKD-aP)***

In July 2018, we announced the dosing of the first patients in a Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in stage III - V (moderate-to-severe) CKD patients. The Phase 2, multicenter, randomized, double-blind, placebo-controlled 12-week trial is designed to evaluate the safety and efficacy of three tablet strengths (0.25 mg, 0.5 mg and 1 mg, once daily administration) of Oral KORSUVA (CR845/difelikefalin) versus placebo in approximately 240 stage III - V (moderate to severe) CKD patients with moderate-to-severe pruritus, with a pre-specified interim assessment that allows for expansion of the study to up to 480 patients, if needed. The primary efficacy endpoint is the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 12 of the treatment period. Secondary endpoints include change from baseline in itch-related quality of life scores at the end of week 12, as assessed by the total Skindex-10 and 5-D itch scores, as well as the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour worst itching NRS score at week 12.

In July 2019, we announced that, based on the recommendation of the IDMC, the ongoing Phase 2 trial would continue as planned with no changes to the original enrollment target of 240 patients. The IDMC's recommendation was based on the results of a pre-specified interim conditional power assessment conducted after approximately 50% of the targeted patient number completed the designated 12-week treatment period. We also announced that the target enrollment had been reached.

The dosing of the above Phase 2 trial was informed by the results of our Phase 1 trial of Oral KORSUVA (CR845/difelikefalin) in patients with Stage III - V CKD. Data from the Phase 1 trials were used to assess the PK and safety of different tablet strengths of Oral KORSUVA (CR845/difelikefalin) (0.25 mg, 0.5 mg and 1.0 mg), dosed daily over a one-week treatment period in patients with moderate and severe renal impairment. The exposure levels achieved with Oral KORSUVA (CR845/difelikefalin) tablets were approximately equivalent to the exposure level achieved with 0.5 mcg/kg dose of KORSUVA (CR845/difelikefalin) injection that exhibited statistically significant and clinically meaningful reduction in itch intensity in hemodialysis patients with moderate to severe CKD-aP in a previous Phase 2 trial.

In December 2019, we announced top-line data from the Phase 2 dose-ranging trial. Patients treated with the 1.0 mg tablet strength of Oral KORSUVA (CR845/difelikefalin) achieved the primary endpoint of statistically significant reduction in weekly mean of the daily worst itching NRS scores vs. placebo after the 12-week treatment period (-4.4 KORSUVA vs. -3.3 placebo, p=0.018). The treatment was statistically significant after two weeks of treatment and sustained through the 12-week treatment period. Regarding secondary endpoints, the proportion of patients on 1.0 mg tablet strength achieving a 3 point or greater improvement from baseline in the weekly mean of the daily worst itching NRS score at week 12 was 72% vs. 58% for placebo but did not achieve statistical significance. Furthermore, patients on 1.0 mg tablet strength showed positive improvements vs. placebo in itch quality of life endpoints as measured using self-assessment Skindex-10 and 5-D Itch scales but did not achieve statistical significance. Oral KORSUVA (CR845/difelikefalin) was generally well-tolerated with a safety profile consistent with that seen in earlier KORSUVA clinical trials. Overall, the incidence of treatment AEs were similar across KORSUVA and placebo groups. The most common AEs reported in >5% of patients in the 1.0 mg KORSUVA group vs. placebo were dizziness (7.5% KORSUVA vs. 0% placebo), fall (6% KORSUVA vs. 0% placebo), diarrhea (6% KORSUVA vs. 1.5% placebo) and constipation (6% KORSUVA vs. 3% placebo).

We plan to conduct an End of Phase 2 Meeting with the FDA with the aim of initiating a Phase 3 program for Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in stage III - V (moderate-to-severe) CKD patients in the second half of 2020.

***Oral KORSUVA (CR845/Difelikefalin) for Treatment of Chronic Liver Disease-Associated Pruritus (CLD-aP)***

Pruritus is a common and serious symptom in patients with CLD, especially those with chronic cholestatic disease. Severe pruritus can have debilitating effects and can lead to a significant reduction in a patient's quality of life. Although the pathogenesis of CLD-aP remains poorly understood, it is likely multifactorial including evidence for an imbalance in the endogenous opioid system driven by higher mu receptor activation (pruritic) versus kappa receptor activation (antipruritic). Consequently, the use of selective kappa-opioid receptor agonists has been suggested for the treatment of pruritus in patients with CLD.

In June 2019, we announced the initiation of a Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in patients with hepatic impairment due to PBC. Pruritus is a common symptom with a prevalence of up to 70% in patients with PBC. The Phase 2 multicenter, randomized, double-blind, placebo-controlled 16-week trial is designed to evaluate the safety and efficacy of 1 mg tablet of Oral KORSUVA (CR845/difelikefalin) taken twice daily or BID versus placebo in approximately 120 patients with PBC and moderate-to-severe pruritus. The primary efficacy endpoint is the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 16 of the treatment period. Secondary endpoints include change from baseline in itch-related quality of life scores at the end of week 16 as assessed by the Skindex-10 and 5-D itch scales, as well as the assessment of proportion of patients achieving an improvement from baseline of ≥3 points with respect to the weekly mean of the daily 24-hour worst itching NRS score at week 16. We continue to screen patients in this ongoing Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) and aim to have top-line data in 2020.

The dose of 1 mg BID in the Phase 2 trial is based on comparison to the exposure levels achieved with 0.5 mcg/kg dose of KORSUVA (CR845/difelikefalin) injection that exhibited statistically significant and clinically meaningful reduction in itch intensity in hemodialysis patients with moderate-to-severe pruritus in the Phase 2 and 3 trials.

In the fourth quarter of 2017, we submitted an investigational new drug application, or IND, to the FDA for Oral KORSUVA (CR845/difelikefalin) for the symptomatic relief of CLD-aP and initiated a Phase 1 safety and PK clinical trial of Oral KORSUVA (CR845/difelikefalin) in patients with CLD in the first quarter of 2018. The open-label study was designed to evaluate the safety and PK profile of repeated doses of Oral KORSUVA (CR845/difelikefalin) taken twice daily in up to 60 patients with CLD and up to 12 matched healthy control subjects. Oral KORSUVA (CR845/difelikefalin) was evaluated over an eight-day treatment period in patients with CLD based on their Child-Pugh classification (i.e., Class A, B and C). The study is now complete. The PK parameters were dose-proportional in patients with mild-to-moderate CLD and Oral KORSUVA (CR845/difelikefalin) was generally well tolerated with no unexpected safety signals reported.

***Oral KORSUVA (CR845/difelikefalin) for Treatment of Moderate-to-Severe Pruritus Associated with Atopic Dermatitis (AD)***

In July 2019, we initiated a Phase 2 randomized, double-blind, placebo-controlled trial that is designed to evaluate the efficacy and safety of Oral KORSUVA (CR845/difelikefalin) for moderate-to-severe pruritus in approximately 240 adult subjects with AD. Subjects will be randomized to three tablet strengths of Oral KORSUVA (CR845/difelikefalin): 0.25 mg, 0.5 mg and 1 mg twice daily versus placebo for 12 weeks followed by a 4-week active extension phase. The primary efficacy endpoint is the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 12 of the treatment period. Secondary endpoints include change from baseline in itch-related quality of life scores at the end of week 12 as assessed by the total Skindex-10 and 5-D itch scales, and itch related Sleep Quality Assessment. Safety endpoints used to evaluate the overall safety and tolerability of Oral KORSUVA (CR845/difelikefalin) will also be included.

In January 2020, we expanded this Phase 2 trial to include approximately 320 adult AD patients with moderate-to-severe pruritus and incorporated an interim conditional power assessment into the design, to be conducted after approximately 50% of the targeted patient number complete the designated 12-week treatment period. Based on current sample size and ongoing enrollment rates, we expect to complete the interim statistical analysis in the second quarter of 2020 and aim to report the top-line results from this trial in 2020.

***Intravenous CR845/Difelikefalin for Treatment of Acute Postoperative Pain***

We also investigated CR845/difelikefalin for the treatment of pain in an acute care setting. CR845/difelikefalin is designed to provide pain relief without stimulating mu opioid receptors and therefore potentially without mu opioid-related side effects, such as nausea, vomiting, respiratory depression and euphoria.

*Phase 2/3 Efficacy and Safety Trial of CR845/Difelikefalin Injection in Patients Undergoing Abdominal Surgery*

In June 2018, we reported positive top-line date from the adaptive Phase 2/3 study of CR845/difelikefalin in patients undergoing abdominal surgery. This trial was initiated in September 2015 and was designed as a multi-center, randomized, double-blind, placebo-controlled, parallel-group adaptive design trial with repeated doses of CR845/difelikefalin injection or placebo administered both prior to and following abdominal surgery. The trial protocol initially included three dose levels of CR845/difelikefalin injection (1.0 mcg/kg, 2.0 mcg/kg and 5.0 mcg/kg versus placebo) that was subsequently modified in June 2016 to test two doses of I.V. CR845/difelikefalin (1.0 mcg/kg and 0.5 mcg/kg) versus placebo, based on a safety review by us, the trial's IDMC, and the FDA, of unblinded safety data from the first 90 patients dosed. The safety review was conducted in response to a clinical hold that the FDA placed on the trial in February 2016 and removed in April 2016 following the safety review. The clinical hold was based on a pre-specified stopping rule related to elevated serum sodium levels of greater than 150 mmol/L that was included in the clinical trial protocol. The trial enrolled 444 patients undergoing abdominal surgery, composed of 228 patients who underwent ventral hernia surgery and 216 patients who completed a hysterectomy procedure. The primary endpoint was pain relief as measured by Area Under the Curve, or AUC, of the NRS pain intensity scores collected over the first 24-hour period after the baseline dose (0 hour) post-surgery for all combined surgeries. The secondary endpoints included incidence of vomiting, improvement in impact scores of PONV, reduction in use of rescue analgesic medication, as well as patient global assessment at 24 hours post baseline dose after surgery.

- CR845 injection achieved statistical significance for the primary endpoint of pain relief over 24 hours (AUC 0-24) post-surgery with the 1.0 mcg/kg dose versus placebo (p=0.032). The 0.5 mcg/kg dose did not achieve statistical significance over the 0-24 hour period (p=0.076). In addition, improvement in pain AUC was statistically significant for both the 0.5 and 1.0 mcg/kg doses over 0 to 6 hours (p=0.041, p=0.001) and 0 to 12 hours (p=0.035, p=0.004) periods and also statistically significant for the 1.0 mcg/kg dose over the 0 to 18-hour period (p=0.013) post-surgery.

- At 6 and 24 hours after baseline dose post-surgery, there were statistically significant improvements in PONV impact scores with both doses of CR845 injection compared to placebo: 0.5 mcg/kg (6 hrs.: p=0.0072, 24 hrs.: p<0.006) and 1.0 mcg/kg (6 hrs.: p<0.0001, 24 hrs.: p<0.0001).

- There were statistically significant differences between placebo and both doses of CR845 with respect to the total use of anti-emetic medication over the first 24 hours post-surgery (0.5 mcg/kg: p=0.0003; 1.0 mcg/kg: p< 0.0001).

- There was a 73% reduction in the incidence of patient-reported vomiting in the group receiving the 1.0 mcg/kg dose versus placebo (p=0.029). Although the 0.5 mcg/kg also showed reduction in vomiting, it did not reach statistical significance. Both doses of CR845 exhibited numerical trends toward reduced use of rescue analgesic medication compared to placebo, but did not achieve statistical significance.

- There was no significant effect, compared to placebo, on patient's global assessment of medication for either dose of CR845 over the 24-hour period.

Common adverse effects reported in the placebo and both CR845 groups were generally low and similar in incidence, and included nausea, constipation, vomiting, flatulence, headache and dyspepsia.

The next steps for the acute post-operative program will be determined after we have completed detailed analysis of the data and consulted with the FDA regarding the regulatory path forward for PONV.

***Human Abuse Liability Trial of CR845/Difelikefalin Injection***

In the fourth quarter of 2014, we successfully completed a Human Abuse Liability, or HAL, trial of CR845/difelikefalin injection. The results from this HAL trial indicate that I.V. CR845/difelikefalin (5 mcg/kg or 15 mcg/kg) demonstrates statistically significant lower "drug liking" scores as measured by VAS Emax ($p < 0.0001$) when compared to I.V. pentazocine (0.5 mg/kg), an approved Schedule I.V. opioid receptor agonist. I.V. CR845 also demonstrated highly statistically significant lower "feeling high," "overall liking," and "take drug again" scores ($p < 0.0001$) as compared to pentazocine. Additionally, CR845/difelikefalin injection showed no "drug liking" dose response as both doses of CR845/difelikefalin injection exhibited similar responses and were not different from placebo injection. Those scores represent standard subjective measures recommended by the FDA to assess a drug's abuse liability. We believe that the totality of the results from the HAL trial are supportive of the potential for CR845/difelikefalin to be the first non-scheduled or low (Schedule V) scheduled peripheral kappa opioid for pruritus or additional indications.

***Respiratory Safety Phase 1 Trial of CR845/Difelikefalin Injection***

In April 2017, we announced summary results from our quantitative Phase 1 trial evaluating respiratory safety of CR845/difelikefalin injection. Respiratory depression remains the most life-threatening side effect of traditional, centrally acting, opioid analgesics, the most commonly used drug class for current treatment of postoperative pain in the United States. The Phase 1 trial was a randomized, double-blind, placebo-controlled, three-way crossover trial of two doses of CR845/difelikefalin injection versus placebo on three measures of respiratory drive in 15 healthy volunteers. Each subject was randomized to one of three treatment sequences and was administered I.V. bolus placebo, I.V. CR845/difelikefalin (1.0 mcg/kg) and I.V. CR845/difelikefalin (5.0 mcg/kg) on sequential 24-hour periods, with I.V. CR845/difelikefalin (5.0 mcg/kg) representing a projected five-fold supra-therapeutic dose. After each administration, and continuing through four hours post-dosing, end-tidal $CO_2$, or $ETCO_2$, oxygen saturation, or $SpO_2$, and respiratory rate were continuously monitored. The primary safety endpoints were: a >10 mmHg sustained ($\geq$30 seconds duration) increase in $ETCO_2$ above baseline or to >50 mmHg, and a sustained reduction in $SpO_2$ to <92%.

There were no statistically significant differences in any respiratory measures observed between groups throughout the four-hour observation period post-dosing and no individual subject met the threshold for a respiratory safety event. Additionally, all treatment-emergent adverse events were previously reported with CR845/difelikefalin administration and were mild, resolving without intervention.

**Collaboration and License Agreements**

*Vifor Fresenius Medical Care Renal Pharma Ltd.*

In May 2018, we entered into a license agreement, or the VFMCRP Agreement, with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, under which we granted VFMCRP a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients worldwide (excluding the United States, Japan and South Korea). We retain full development and commercialization rights for KORSUVA injection for the treatment of CKD-aP in dialysis patients in the U.S. except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where we and VFMCRP will promote KORSUVA injection under a profit-sharing arrangement.

Upon entry into the VFMCRP Agreement, VFMCRP made a non-refundable, non-creditable $50 million upfront payment to us and Vifor (International) Ltd., or Vifor, purchased 1,174,827 shares of our common stock for $20 million, at a premium for the price of $17.024 per share. In addition, we are eligible to receive from VFMCRP regulatory and commercial milestone payments in the aggregate of up to $470 million, consisting of up to $30 million in regulatory milestones and up to $440 million in tiered commercial milestones, all of which are sales-related. We are also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined, of KORSUVA (CR845/difelikefalin) injection in the licensed territories. In the United States, we and VFMCRP will promote KORSUVA

(CR845/difelikefalin) injection in the dialysis clinics of FMCNA under a profit-sharing arrangement (subject to the terms and conditions of the VFMCRP Agreement) based on net FMCNA clinic sales recorded by us.

*Maruishi Pharmaceutical Co., Ltd.*

In April 2013, we entered into a license agreement with Maruishi, or the Maruishi Agreement, under which we granted Maruishi an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in Japan in the acute pain and uremic pruritus fields. Maruishi has a right of first negotiation for any other indications for which we develop CR845/difelikefalin and, under certain conditions, Maruishi may substitute another pruritus indication for the uremic pruritus indication originally included in its license from us. If we abandon development of CR845/difelikefalin and begin development of another kappa opioid receptor agonist that is covered by the claims of the patents we licensed to Maruishi, such other agonist will automatically be included in the license to Maruishi. Maruishi is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in Japan. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States.

Under the terms of the Maruishi Agreement, we received a non-refundable and non-creditable upfront license fee of $15.0 million and are eligible to receive up to an aggregate of $10.5 million in clinical development and regulatory milestones. In August 2014, we received a milestone payment of $0.5 million upon the completion by Maruishi of a Phase 1 clinical trial in Japan related to CR845/difelikefalin in acute post-operative pain. In September 2015, Maruishi initiated a Phase 2 clinical trial of CR845/difelikefalin in Japan for uremic pruritus, which triggered a $1.7 million milestone payment (net of contractual foreign currency exchange adjustments of $0.3 million) to us. In March 2017, we received a payment of $0.8 million from Maruishi when it entered into a sub-license agreement with Kissei related to CR845/difelikefalin. We are also eligible to receive a one-time sales milestone of one billion Yen when a certain sales level is attained. We also receive a mid-double-digit percentage of all non-royalty payments received by Maruishi from its sublicensees, if any. We are also eligible to receive tiered royalties based on net sales, if any, with minimum royalty rates in the low double digits and maximum royalty rates in the low twenties. Maruishi's obligation to pay us royalties continues, on a product-by-product basis, until the expiration of the last-to-expire licensed patent covering such product or the later expiration of any market exclusivity period. The Maruishi Agreement continues until terminated. Either we or Maruishi may terminate the Maruishi Agreement for the other party's breach of the agreement or bankruptcy. Maruishi may terminate the agreement at any time at will. We may terminate the agreement as a whole if Maruishi challenges the licensed patent rights, and we may terminate the agreement with respect to any indication if Maruishi discontinues its development activities. In addition, in connection with the license agreement, Maruishi made an $8.0 million equity investment in our company.

*Chong Kun Dang Pharmaceutical Corporation*

In April 2012, we entered into a license agreement with CKDP, or the CKDP Agreement, under which we granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in South Korea. CKDP is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in South Korea. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States.

Under the terms of the CKDP Agreement, we received a non-refundable and non-creditable $0.6 million upfront payment and are eligible to earn up to an aggregate of $3.8 million in development and regulatory milestones. In addition, in connection with the CKDP Agreement, CKDP made a $0.4 million equity investment in our company. We will also receive a mid-double-digit percentage of all non-royalty payments received by CKDP from its sublicensees, if any. We are also eligible to receive tiered royalties ranging from the high single digits to the high teens based on net sales, if any. CKDP's obligation to pay us royalties continues, on a product-by-product basis, until the expiration of the last-to-expire licensed patent covering such product or the later expiration of any market exclusivity period.

During 2012, we received an additional $0.6 million, net of foreign taxes, from CKDP upon the achievement of two clinical development milestones under the CKDP Agreement. During 2015, we received a total of $0.6 million, net

of foreign taxes, from CKDP upon the achievement of two clinical development milestones under the CKDP Agreement. The CKDP Agreement continues until CKDP no longer has any obligation to pay us royalties on any product. Either we or CKDP may terminate the CKDP Agreement for the other party's breach of the CKDP Agreement or bankruptcy. CKDP may terminate the CKDP Agreement if any of the licensed patent rights is invalid, unenforceable, is narrowed in scope or is deemed unpatentable, except as a result of a challenge by CKDP, or a third party commercializes a product containing a compound identical to CR845/difelikefalin without infringing any of the licensed patent rights in South Korea. We may terminate the CKDP Agreement if CKDP challenges the licensed patent rights or if a third party in South Korea owns an issued patent that claims CR845/difelikefalin and CKDP's sale of products would infringe that patent.

**Manufacturing and License Agreements**

*Enteris Biopharma, Inc.*

On August 20, 2019, we entered into the Enteris License Agreement. Pursuant to the Enteris License Agreement, Enteris granted to us a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

As consideration for the licensed rights under the Enteris License Agreement, we paid an upfront fee equal to $8.0 million, consisting of $4.0 million in cash and $4.0 million in shares of our common stock pursuant to the Purchase Agreement described below.

We are also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low-single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, we have the right, but not the obligation, to terminate our obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. Subject to certain conditions, we may elect to pay 50% of the lump sum due under the Royalty Buyout in shares of our common stock pursuant to the Purchase Agreement.

The Enteris License Agreement will expire on a country-by-country, licensed product-by-licensed product basis upon the later of (1) the expiration (or invalidation) of all valid claims in licensed patent rights that cover such product in such country, (2) the end of the calendar quarter in which generic competition (as defined in the Enteris License Agreement) occurs for such product in such country and (3) ten years from the first commercial sale of such product.

Either party may terminate the Enteris License Agreement upon written notice if the other party has failed to remedy a material breach within 60 days (or 30 days in the case of a material breach of a payment obligation). Enteris may terminate the Enteris License Agreement upon 30 days' written notice to us if we or any of our affiliates formally challenge the validity of any licensed patent rights or assists a third party in doing so. We may terminate the Enteris License Agreement for any reason or no reason (a) prior to receipt of first regulatory approval for a licensed product in the United States for any indication upon 30 days' prior written notice to Enteris or (b) on or after receipt of first regulatory approval for a licensed product in the United States for any indication upon 60 days' prior written notice to Enteris.

In connection with the Enteris License Agreement, on August 20, 2019, we entered into the Purchase Agreement with Enteris and its affiliate, EBP Holdco LLC, collectively referred to as Purchaser, pursuant to which we issued and sold to Purchaser 170,793 shares of our common stock in a private placement. Such shares were issued in satisfaction of the $4.0 million portion of the upfront fee payable in shares of our common stock pursuant to the Enteris License Agreement and for no additional consideration, based on a purchase price of $23.42 per share, which was equal to the 30-day volume weighted average price of our common stock on August 20, 2019. In addition, if we exercise our Royalty Buyout option, we may elect to make 50% of the payment in stock by issuing additional shares of our common stock

valued at the 30-day volume weighted average price of our common stock as of such exercise. Pursuant to the Purchase Agreement, we effected the registration and sale of the shares issued and sold to Purchaser thereunder in accordance with the applicable requirements of the Securities Act of 1933, as amended, or the Securities Act, which included the filing of a registration statement with the SEC on September 9, 2019. In addition, the Purchase Agreement includes customary representations, warranties and covenants by us.

*Patheon UK Limited*

On July 8, 2019, we entered into an MSA with Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to us for the drug products specified by us from time to time. Pursuant to the MSA, we have agreed to order from Patheon at least a certain percentage of our commercial requirements for a product under a related Product Agreement. Each Product Agreement that we may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement.

The MSA has an initial term ending December 31, 2023, and will automatically renew after the initial term for successive terms of two years each if there is a Product Agreement in effect, unless either party gives notice of its intention to terminate the MSA at least 18 months prior to the end of the then current term.

Either party may terminate the MSA or a Product Agreement upon written notice if the other party (1) has failed to remedy a material breach within a specified time or (2) is declared insolvent or bankrupt, voluntarily files a petition of bankruptcy or assigns such agreement for the benefit of creditors. We may terminate a Product Agreement (a) upon 90 days' prior written notice if any governmental agency takes any action that prevents us from selling the relevant product in the relevant territory, (b) upon six months' prior written notice if we do not intend to order manufacturing services due to a product's discontinuance in the market, or (c) upon 90 days' prior written notice if we determine that the manufacture or supply of a product likely infringes third-party rights. Patheon may terminate the MSA or a Product Agreement (i) upon six months' prior written notice if we assign such agreement to an assignee that is unacceptable to Patheon for certain reasons, or (ii) upon 30 days' prior written notice if, after the first year of commercial sales, we forecast zero volume for 12 months.

The MSA contains, among other provisions, customary representations and warranties by the parties, a grant to Patheon of certain limited license rights to our intellectual property in connection with Patheon's performance of the services under the MSA, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions.

On July 8, 2019, and July 9, 2019, we entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of CR845/difelikefalin injection, our lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of CR845/difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from active pharmaceutical ingredient supplied by us. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product.

**Sales and Marketing**

In executing our strategy, our goal is to have significant control over the development process and commercial execution for CR845/difelikefalin in the United States, if approved.

We anticipate developing a distribution capability and commercial organization in the United States to market and sell KORSUVA (CR845/difelikefalin) injection, if approved, in the dialysis setting, while out-licensing commercialization rights in certain geographical territories outside of the United States. For Oral KORSUVA (CR845/difelikefalin), we plan to develop and commercialize our drug candidate in pruritus indications, such as CKD-aP, CLD-aP and potentially others, on our own in the United States, while exploring partnerships for development and commercialization in geographical territories outside the United States.

In 2015, we commissioned a qualitative market research study of nephrologists to evaluate the commercial potential of KORSUVA (CR845/difelikefalin) for CKD-aP. The study suggests KORSUVA (CR845/difelikefalin) would be well received by nephrologists, if approved. The key findings from the study were:

- There is a clear unmet need to manage CKD-aP among dialysis patients.
- Currently, there are no effective options for severe CKD-aP.
- CR845/difelikefalin demonstrates impressive efficacy for CKD-aP.
- Physicians were impressed with placebo-like adverse event profile.
- KORSUVA (CR845/difelikefalin) injection can easily be incorporated into dialysis sessions.

As a result, we believe that, if successful, KORSUVA (CR845/difelikefalin) is well positioned to address the unmet needs for hemodialysis patients suffering from CKD-aP.

We had also commissioned market research for I.V. CR845/difelikefalin for the treatment of PONV that suggests it would be well received by physicians, if approved. This research indicated that anesthesiologists rated efficacy in high-risk patients and the scarcity of rescue medications as the highest unmet needs. There is an opportunity for greater efficacy in high-risk patients who typically receive three or more products prophylactically. Anesthesiologists stated the most favorable attributes of CR845 included its novel mechanism of action, positive efficacy results and favorable side effect profile. The novel mechanism of action was favorable given its potential additive effect on existing multimodal treatment regimens as well as its potential as a new option for rescue therapy, a therapy that is used when prophylactic agents have failed to prevent nausea and vomiting. Anesthesiologists indicated a preference to utilize CR845 in combination with existing regimens for high-risk patients particularly in invasive surgeries that require narcotics. In our three Phase 2 trials, I.V. CR845/difelikefalin demonstrated statistically significant reductions in PONV as well as statistically significant reductions in pain relief. As a result, we believe that, if successful, I.V. CR845/difelikefalin is well positioned to address unmet needs in the PONV market.

**Intellectual Property**

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technology and other inventions that are important to our business. As more fully described below, patent applications have been filed covering compositions of matter for and novel formulations of these compositions, as well as methods of using CR845/difelikefalin. Twelve U.S. patents directed to CR845/difelikefalin and its uses have been issued, which are expected to expire no earlier than 2027. Additionally, three other U.S. patents have been granted with claims to CR845/difelikefalin-like compounds and their uses. We have filed patent applications in the U.S. and internationally claiming novel oral formulations of CR845/difelikefalin, which if granted would be expected to expire no earlier than 2039. We also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, and continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of peripheral analgesia and treatment of pruritus.

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

commercially reasonable terms, or our business could be harmed, possibly materially. If we were not able to obtain a license or were not able to obtain a license on commercially reasonable terms, our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to novel peripheral analgesics, novel formulations and novel uses of our proprietary compounds. We anticipate seeking patent protection in the United States and internationally for the chemistries and processes for manufacturing these compounds and novel formulations and uses of these compounds in a variety of therapies.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and the patent's scope can be modified after issuance by later judicial decisions. Consequently, we do not know whether any of our product candidates will be adequately protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for up to 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of our entitlement to the inventions covered by pending patent applications. Moreover, although unlikely, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or USPTO, to determine priority of invention, or in post-grant challenge proceedings in the USPTO, or a foreign patent office such as oppositions, inter-partes review, post grant review, or a derivation proceeding, that challenge our entitlement to an invention or the patentability of one or more claims in our patent applications or issued patents. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

The patent portfolios for our most advanced programs are summarized below.

***CR845/Difelikefalin***

Our synthetic peptide amide kappa opioid agonist patent portfolio is wholly owned by us. The portfolio includes fifteen issued U.S. patents (U.S. Patent Nos. 7,402,564; 7,713,937; 7,727,963; 7,842,662; 8,217,007; 8,236,766; 8,486,894; 8,536,131; 8,906,859; 8,951,970; 9,321,810; 9,334,305; 9,359,399; 10,017,536; and 10,138,270) with claims to compositions of a wide range of synthetic peptide amide kappa opioid agonists, including CR845/difelikefalin and related molecules, as well as methods of using these compounds. U.S. Patent No. 7,402,564, which is the earliest issued U.S. patent claiming CR845/difelikefalin compositions is due to expire November 12, 2027, although the patent term is expected to be extended for up to a further five (5) years, i.e. to November 12, 2032, based upon the Hatch-Waxman Act. The CR845/difelikefalin patent portfolio also includes pending U.S. patent applications which claim additional uses and methods of administering CR845/difelikefalin. Related foreign applications were filed in more than 40 other countries. National patents have been granted in 31 European countries, as well as in Australia, Brazil, Canada, China, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Russia, Singapore, South Africa and South Korea. These granted foreign patents with claims to CR845/difelikefalin are due expire no earlier than November 12, 2027. The Brazilian patent law provides for a patent term extension of up to ten years for pharmaceutical patents to compensate for the loss of patent term during prosecution.

***Other Cara Patents and Patent Applications***

We also own several other U.S. Patents including U.S. Patent Nos. 7,741,350; 7,960,376; 7,960,377; and 8,211,926 with claims to other cannabinoid compounds and U.S. Patent No. 8,217,000 with claims to regulation of prolactin in mammals including humans.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a PCT application or a non-provisional patent application. The term of a patent in the United States can be adjusted and extended due to the

failure of the United States Patent and Trademark Office following certain statutory and regulation deadlines for progressing prosecution and issuing a patent.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for a portion of the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. Although we intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development, or R&D, or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

**Competition**

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, and medical technology companies. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a large number of companies developing or marketing therapies for the indications that we are pursuing. Many of our competitors, including many of the organizations named below, have substantially greater financial, technical and human resources than we do and significantly greater experience in the development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of competitors. Small or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. We also compete with these companies in recruiting and retaining qualified scientific personnel and establishing clinical trial sites and patient registration for clinical trials.

We believe the key competitive factors that will affect the development and commercial success of our product candidates, if approved for marketing, are likely to be their safety, efficacy and tolerability profile, reliability, convenience of dosing, price and reimbursement from government and third-party payers. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain

approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. Generic products that broadly address these indications are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

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

***KORSUVA (CR845/difelikefalin) injection - Uremic Pruritus or CKD-aP.*** We are developing KORSUVA (CR845/difelikefalin) injection for the management of CKD-aP in hemodialysis patients. Currently, there are no approved products for management of CKD-aP in the United States. However, there are many products that are used to help manage CKD-aP. 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 gabapentin or naltrexone, generally with limited success or therapies such as UVB light therapy with limited availability.

Because of the substantial unmet need for products that are safe and effective in CKD-aP, there are other companies that either were in the past or are currently involved in the discovery, development, and/or marketing of such products for CKD-aP or related conditions. Some of such product candidates or products include SK-1405 from Sanwa Kagaku Kenkyusho and Remitch® or nalfurafine from Toray Industries.

***Oral KORSUVA (CR845/difelikefalin) – Chronic Pruritus.*** We are developing Oral KORSUVA (CR845/difelikefalin) for the management of moderate-to-severe chronic pruritus conditions like CKD-aP or CLD-aP. There are currently no products approved in the United States for CKD-aP or CLD-aP. The market for the management of moderate-to-severe chronic pruritus is highly fragmented and includes numerous generic products, including oral formulations of corticosteroids and antihistamines. The most common corticosteroids and antihistamines are available generically. Because of the size and untapped potential of the chronic pruritus market and the substantial unmet need for products that are safe and effective, there are other companies involved in the discovery, development, and/or marketing of new products for pruritus. Some product candidates being developed for pruritus or pruritic conditions include Menlo Therapeutics' serlopitant, Trevi's nalbuphine ER and Vanda's tradipitant.

***I.V. CR845/difelikefalin – Post-Operative Nausea and Vomiting (PONV) Management.*** The market for the prevention and treatment of PONV is highly fragmented. Anesthesiologists utilize a number of different agents alone or in combination (particularly in patients with a high risk for PONV) with different mechanism of actions to try to manage PONV. If approved, I.V. CR845/difelikefalin would likely be competing within the overall PONV market, although we expect that it would primarily be utilized as an add-on therapy in patients with a higher risk of PONV. Although most of the PONV products are generically available, there is still a significant segment of high-risk patients where their PONV is not adequately managed, which can increase the hospital length of stay and add significant cost to managing a post-operative patient.

**Manufacturing**

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. At this time, none of our contract manufacturing agreements limit where, or with whom we can contract for commercial manufacture or distribution. It is our intention that by the time of any regulatory approvals for commercialization, we will have negotiated long-term commitments with at least one primary supplier for each manufacturing and distribution function. At this time, we have entered into a non-exclusive commercial manufacturing agreement with Patheon for KORSUVA (CR845/difelikefalin) injection.

All of our product candidates are either small peptides or organic small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and

does not require any special equipment or technology in the manufacturing process. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

**Government Regulation and Product Approval**

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

***FDA Regulation***

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of human clinical trials, including adequate and well-controlled clinical trials, in accordance with good clinical practices, or cGCP, to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine cGCP compliance;
- FDA review and approval of the NDA; and
- potential DEA review and scheduling activities prior to launch for some of our product candidates.

***Preclinical Studies.*** Preclinical studies include laboratory evaluation of drug substance chemistry, toxicity and drug product formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Manufacture of drug substance, drug product and the labeling and distribution of clinical supplies must all comply with cGMP standards. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

***Clinical Trials.*** Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with cGCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at 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 continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

***Marketing Approval.*** Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug 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. 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.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to mitigate any identified or suspected serious risks and ensure safe use of the drug. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an external advisory committee. 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.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. 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 trial sites to assure compliance with cGCP.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. For some products, an additional step of DEA review and scheduling is required.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some 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.

***Breakthrough Therapy Designation.*** The FDA may expedite the review of a product candidate designated as a breakthrough therapy, which is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial

improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A sponsor may request the FDA to designate a drug as a breakthrough therapy at the time of, or any time after, the submission of an IND application for the drug. If the FDA designates a drug as a breakthrough therapy, it must take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the drug; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment. The FDA may rescind a Breakthrough Therapy designation in the future if further clinical development later shows that the criteria for designation are no longer met. Breakthrough Therapy designation does not change the standards for approval, but may expedite the development or review process.

***Post-Approval Requirements.*** Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion, reporting of adverse experiences with the product, and compliance with any post-approval requirements imposed as a condition of approval, such as Phase 4 clinical trials and surveillance to assess safety and effectiveness after commercialization. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products, as well as new application fees for supplemental applications with clinical data. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards 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 mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new 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 NDAs or supplements to approved NDAs, 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 marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

***DEA Regulation***

I.V. CR845/difelikefalin, Oral CR845/difelikefalin or any of our future product candidates, if approved, may be regulated as a "controlled substance" as defined in the Controlled Substances Act of 1970, or CSA, which establishes registration, security, recordkeeping, reporting, storage, distribution and other requirements administered by the DEA. The DEA is concerned with the control of handlers of controlled substances, and with the equipment and raw materials used in their manufacture and packaging, in order to prevent loss and diversion into illicit channels of commerce.

The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. The manufacture, shipment, storage, sale and use of Schedule II substances are subject to a high degree of regulation.

Annual registration is required for any facility that manufactures, distributes, dispenses, imports or exports any controlled substance. The registration is specific to the particular location, activity and controlled substance schedule. For example, separate registrations are needed for import and manufacturing, and each registration will specify which schedules of controlled substances are authorized.

The DEA typically inspects a facility to review its security measures prior to issuing a registration. Security requirements vary by controlled substance schedule, with the most stringent requirements applying to Schedule I and Schedule II substances. Required security measures include background checks on employees and physical control of inventory through measures such as cages, surveillance cameras and inventory reconciliations. Records must be maintained for the handling of all controlled substances, and periodic reports made to the DEA, for example distribution reports for Schedule I and II controlled substances, Schedule III substances that are narcotics, and other designated substances. Reports must also be made for thefts or losses of any controlled substance, and to obtain authorization to destroy any controlled substance. In addition, special authorization and notification requirements apply to imports and exports.

In addition, a DEA quota system controls and limits the availability and production of controlled substances in Schedule I or II. Distributions of any Schedule I or II controlled substance must also be accompanied by special order forms, with copies provided to the DEA. The DEA may adjust aggregate production quotas and individual production and procurement quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments. Our quota of an active ingredient may not be sufficient to meet commercial demand or complete clinical trials. Any delay or refusal by the DEA in establishing our quota for controlled substances could delay or stop our clinical trials or product launches.

To meet its responsibilities, the DEA conducts periodic inspections of registered establishments that handle controlled substances. Individual states also regulate controlled substances, and we and our collaborators will be subject to state regulation with respect to the distribution of these products.

***Fraud and Abuse, Data Privacy and Security and Transparency Laws and Regulations***

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state health care regulatory laws restrict business practices in the biopharmaceutical industry. These laws include, among other things, anti-kickback and false claims laws and regulations, physician payment transparency laws and regulations, as well as data privacy and security laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances.

Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act (collectively, the “Health Care Reform Law”), to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the Health Care Reform Law provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

Federal false claims laws, including the federal civil False Claims Act prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes “any request or demand” for money or property presented to the U.S. government. The federal civil False Claims Act has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion of off-label uses not expressly approved by FDA in a drug’s label, and allegations as to misrepresentations with respect to the services rendered. Additionally, the civil monetary penalties statute, which, among other things, imposes fines against any person or entity who is determined to have presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, including private third-party payers and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services relating to healthcare matters. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and

Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, imposes specified requirements on certain types of individuals and entities subject to the law, known as covered entities, such as certain healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that process individually identifiable health information on their behalf, relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes security standards and certain privacy standards directly applicable to the business associates of covered entities that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws may govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, federal transparency laws, including the federal Physician Payments Sunshine Act created under Section 6002 of the Health Care Reform Law and its implementing regulations, require that manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made or distributed to physicians (defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors), generally, with some exceptions, and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals. Additionally, applicable manufacturers and applicable group purchasing organizations are required to report annually to CMS certain ownership and investment interests held by physicians (as defined above) and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse-midwives.

There are also an increasing number of analogous state laws that require manufacturers to file reports with states on pricing and marketing information, such as tracking and reporting of gifts, compensations, other remuneration and items of value provided to healthcare professionals and healthcare entities. Many of these laws contain ambiguities as to what is required to comply with such laws. For example, several states have enacted legislation requiring pharmaceutical companies to, among other things, establish and implement commercial compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities and/or register their sales representatives. Certain state laws also regulate manufacturers' use of prescriber-identifiable data. These laws may affect our future sales, marketing and other promotional activities by imposing administrative and compliance burdens. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions once we commercialize could be subject to the penalty provisions of the pertinent state and federal authorities.

If our operations are found to be in violation of any of the health regulatory laws described above or any other laws that apply to us, we may be subject to penalties, including significant criminal, civil and administrative penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

*Coverage and Reimbursement Generally*

The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental payer programs at the federal and state

levels, including Medicare and Medicaid, private health insurers and other third-party payers provide coverage for and establish adequate reimbursement levels for our product candidates. In the United States, private health insurers and other third-party payers often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services.

In the United States, the European Union and other potentially significant markets for our product candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and utilization, which may adversely affect our future product sales and results of operations. For example, 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 cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2020 contains additional drug price control measures that could be enacted during the budget process or in other future legislation such as 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. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services, or HHS, has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Although a number of these, and other measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented 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, to encourage importation from other countries and bulk purchasing. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payers to reimburse all or part of the associated healthcare costs. In addition, many U.S. hospitals receive a fixed reimbursement amount per procedure for certain surgeries and other treatment therapies they perform, or a predetermined rate for all hospital inpatient care provided as payment in full. Because this amount may not be based on the actual expenses the hospital incurs, hospitals may choose to use therapies which are less expensive when compared to our product candidates. Sales of our product candidates will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, such as Medicare and Medicaid, private health insurers and other third-party payers. Third-party payers are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products, including pharmaceuticals. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Additionally, third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Therefore, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. Moreover, a payer's decision to provide coverage for a drug product

does not imply that an adequate reimbursement rate will be approved, and one payer's determination to provide coverage for a product does not assure that other payers will also provide coverage. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payers and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates.

*Healthcare Regulatory Developments*

In the United States and some foreign jurisdictions, the legislative landscape with respect to healthcare continues to evolve. There have been a number of legislative and regulatory changes to the healthcare system that could affect our ability to sell our products profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Health Care Reform Law was passed in March 2010 and includes provisions that have substantially changed healthcare financing by both governmental and private insurers. Among other provisions that could have an impact on our business, the Health Care Reform Law revised the methodology by which rebates owed by manufacturers to the state and federal government for covered outpatient drugs under the Medicaid Drug Rebate Program are calculated, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government's comparative effectiveness research. Additionally, the Health Care Reform Law implemented a new Medicare Part D coverage gap discount program in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the outpatient drugs being covered under Medicare Part D. The Health Care Reform Law's future impact on our business is unclear.

There remains judicial and Congressional challenges to certain aspects of the Health Care Reform Law, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Health Care Reform Law. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the Health Care Reform Law or otherwise circumvent some of the requirements for health insurance mandated by the Health Care Reform Law. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Health Care Reform Law. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Health Care Reform Law have been signed into law. The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Health Care Reform Law on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". In addition, the 2020 federal spending package permanently eliminates, effective January 1, 2020, the Health Care Reform Law's 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. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Health Care Reform Law, effective January 1, 2019, to close the coverage gap in most Medicare drug plans. In December 2018, CMS published a new final rule permitting further collections and payments to and from certain Health Care Reform Law qualified health plans and health insurance issuers under the Health Care Reform Law risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Health Care Reform Law is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the TCJA. Additionally, on December 18, 2019, the U.S. Court of Appeals for the Fifth Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the Health Care Reform Law are invalid as well. It is unclear how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the Health Care Reform Law will impact the Health Care Reform Law.

In addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, as amended, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee on Deficit Reduction did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year starting in 2013 and, following passage of the Bipartisan Budget Act of 2015, and subsequent legislative amendments, including the BBA, will remain in effect until 2029, 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 and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or 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 I 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 pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

These and other healthcare reform initiatives may result in additional reductions in Medicare payments and other healthcare funding, which could have a material adverse effect on our financial operations. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could further limit the prices we are able to charge, or the amounts of reimbursement available, for our product candidates once they are approved.

***Foreign Regulation***

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. For example, in the European Union, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

**Employees**

As of February 24, 2020, we had 67 employees, all of whom are located in the United States. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

**Website Access to Reports**

Our website is *www.caratherapeutics.com*. We are subject to the informational requirements of the Exchange Act and file or furnish reports, including our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Exchange Act, proxy statements and other information with the SEC. We make copies of these reports and other information available free of charge through our website (under the heading "SEC Filings") as soon as reasonably practicable after we file or furnish them with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other

information regarding issuers that file electronically with the SEC at www.sec.gov. The information contained on the websites referenced in this Annual Report on Form 10-K is not incorporated by reference into this filing, and the website addresses are provided only as inactive textual references.

**Item 1A.** ***Risk Factors***

*In addition to other information contained in this Annual Report on Form 10-K, the following risks should be considered in evaluating our business and future prospects and an investment in our common stock. The risks and uncertainties described below are not the only ones we face. If any of the following risks and uncertainties develops into actual events, our business, financial condition, results of operations and cash flows could be materially adversely affected. In that case, the price of our common stock could decline and you may lose all or part of your investment.*

**Risks Related to Our Financial Condition and Capital Requirements**

***We have incurred significant losses since our inception, anticipate that we will incur continued losses for the foreseeable future, and may never achieve or maintain profitability.***

We are a clinical-stage biopharmaceutical company. For the last several years, we have focused our efforts primarily on developing I.V. and Oral CR845/difelikefalin with the goal of achieving regulatory approval. Since inception, we have incurred significant operating and net losses. Our net losses were $106.4 million, $74.0 million and $58.1 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $400.7 million. We expect to continue to incur significant expenses and operating and net losses over the next several years, as we continue to develop and seek marketing approval for I.V. and Oral CR845/difelikefalin. Our net losses may fluctuate significantly from year to year, depending on the timing of our clinical trials, the receipt of additional milestone payments, if any, under our agreements with VFMCRP, Maruishi and CKDP, the receipt of payments under any future agreements we may enter into, and our expenditures on other R&D activities as well as any payments owed under the License Agreement with Enteris and any future similar agreements.

In addition, we expect to incur significant sales, marketing and manufacturing expenses related to the commercialization of I.V. and Oral CR845/difelikefalin, if they are approved by the FDA. As a result, we expect to continue to incur significant losses for the foreseeable future. We anticipate that our expenses will increase significantly as we:

- continue the development of KORSUVA (CR845/difelikefalin) injection for CKD-aP;
- continue the development of Oral KORSUVA (CR845/difelikefalin) for CKD-aP and CLD-aP;
- expand our Oral KORSUVA (CR845/difelikefalin) program into certain dermatologic conditions, including AD;
- explore further development of CR845/difelikefalin injection in the post-operative setting;
- seek regulatory approvals for KORSUVA (CR845/difelikefalin) injection and any other product candidate that successfully completes clinical trials;
- establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval;
- maintain, expand and protect our global intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel; and

- add operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts.

To become and remain profitable, we must succeed in developing and eventually commercializing one or more products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing clinical trials of KORSUVA (CR845/difelikefalin) injection and Oral KORSUVA (CR845/difelikefalin), discovering additional product candidates and completing preclinical testing and clinical trials for those product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We may never succeed in these activities and, even if we do, may never achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA or foreign regulatory authorities, to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

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

***Our operating history makes it difficult to evaluate our business and prospects.***

We commenced operations in 2004, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital and advancing our product candidates, including KORSUVA (CR845/difelikefalin) injection and Oral KORSUVA (CR845/difelikefalin), through clinical development. We have not yet demonstrated an ability to obtain regulatory approval for, or successfully commercialize, a product candidate. If our product candidates are approved by the FDA, we will need to expand our capabilities to support commercial activities. We may not be successful in adding such capabilities. Consequently, any predictions about our future performance may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

***We will need additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.***

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships and successfully manufacturing and commercializing our product candidates is expensive. We will need to raise additional capital to:

- progress our KORSUVA (CR845/difelikefalin) injection CKD-aP program through Phase 3 pivotal trials and NDA filing;
- continue the further development of Oral KORSUVA (CR845/difelikefalin) for CKD-aP and CLD-aP;
- expand our Oral KORSUVA (CR845/difelikefalin) program into certain dermatologic conditions, including AD;
- explore further development of CR845/difelikefalin injection in the post-operative setting;
- fund our operations and continue our efforts to hire additional personnel and build a commercial infrastructure to prepare for the commercialization of KORSUVA (CR845/difelikefalin) injection, if approved by the FDA;

- qualify and outsource the commercial-scale manufacturing of our products, including KORSUVA (CR845/difelikefalin) injection under cGMP; and

- in-license other product candidates.

We believe that with our available cash and cash equivalents and marketable securities balances as of December 31, 2019, we will have sufficient funds to meet our projected operating requirements into the second half of 2021, without giving effect to any potential milestone payments we may receive under our collaboration agreements. We have based this estimate on assumptions that may prove to be wrong and we could spend our available financial resources faster than we currently expect. Further, because we do not have sufficient financial resources to meet all of our development objectives, especially our efforts to build a commercial infrastructure to prepare for the commercialization of KORSUVA (CR845/difelikefalin) injection, if approved, and the completion of our development of Oral KORSUVA (CR845/difelikefalin) for the treatment of CKD-aP and CLD-aP, we will need to raise additional capital. If we are not able to do so, we could be required to postpone, scale back or eliminate some, or all, of these objectives. Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and costs related to our Phase 3 development of KORSUVA (CR845/difelikefalin) injection and Phase 2 development of Oral KORSUVA (CR845/difelikefalin) for CKD-aP, CLD-aP and other indications;

- the rate of progress and costs of our efforts to prepare for the submission of an NDA for KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in hemodialysis patients or for any product candidates that we may in-license or acquire in the future, and the potential that we may need to conduct additional clinical trials to support applications for regulatory approval;

- the costs of establishing a commercial organization to sell, market and distribute KORSUVA (CR845/difelikefalin) injection, if approved;

- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with our product candidates, including any such costs we may be required to expend if our licensors are unwilling or unable to do so;

- the cost and timing of manufacturing sufficient supplies of KORSUVA (CR845/difelikefalin) injection in preparation for commercialization, if approved;

- the effect of competing technological and market developments;

- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish; and

- the success of the commercialization of KORSUVA (CR845/difelikefalin) injection, if approved, and any future product candidates.

Future capital requirements will also depend on the extent to which we acquire or invest in additional complementary businesses, products and technologies. Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings, milestone and royalty payments from corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all. If adequate funds are not available, we may be required to delay, reduce the scope of, or eliminate, one or more of our development programs or our commercialization efforts.

**Risks Related to Our Business and the Development of Our Product Candidates**

***We are substantially dependent on the success of our lead product candidate, KORSUVA (CR845/difelikefalin) injection being developed for the treatment of CKD-aP in hemodialysis patients, and cannot guarantee that this product candidate will successfully complete Phase 3 clinical trials, receive regulatory approval or be successfully commercialized.***

We currently have no products approved for commercial distribution. We have invested a significant portion of our efforts and financial resources in the development of KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in patients undergoing hemodialysis. Our business depends entirely on the successful development and commercialization of our product candidates, and in particular, KORSUVA (CR845/difelikefalin) injection, which may never occur. Our ability to generate product revenues in the near term is dependent on our ability to develop, obtain regulatory approval for, and then successfully commercialize KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in patients undergoing hemodialysis. We currently generate no revenues from sales of any products, and we may never be able to develop or commercialize a marketable product.

In May 2019, we announced positive results from the double blinded phase of the first pivotal Phase 3 efficacy trial (KALM-1) of KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in patients undergoing hemodialysis. This trial was initiated in the first quarter of 2018 in the United States and has entered into the 52-week open label extension phase. In August 2018, we initiated the second pivotal Phase 3 efficacy trial, KALM-2 (with a 52-week open label extension phase) of KORSUVA (CR845/difelikefalin) injection that is expected to enroll patients in the United States and multiple countries outside the United States. In October 2019, we completed an interim statistical assessment of KALM-2 and based on the recommendation of the Independent Data Monitoring Committee, or IDMC, the size of the trial has been increased from the original enrollment target of 350 patients to a new target of 430 patients. In addition to these trials, we are also conducting 52-week and 12-week Phase 3 open label safety studies of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP. Based on the current status of our completed and ongoing efficacy and safety trials, we expect to file the NDA for KORSUVA (CR845/difelikefalin) injection in the second half of 2020. However, we cannot give you any assurance that our Phase 3 trials for KORSUVA (CR845/difelikefalin) injection will be completed within a specified period of time or at all, and if they are completed, we cannot assure you that they will successfully support our regulatory applications for approval.

In addition to clinical development, KORSUVA (CR845/difelikefalin) injection will require regulatory approval, establishment of a commercial organization, significant marketing efforts and further investment before we generate any revenues from product sales. We are not permitted to market or promote any of our product candidates, including KORSUVA (CR845/difelikefalin) injection, before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. If we do not receive FDA approval for, and successfully commercialize KORSUVA (CR845/difelikefalin) injection, we will not be able to generate revenue in the United States in the foreseeable future, or at all. Any significant delays in obtaining approval for and commercializing CR845/difelikefalin injection will have a substantial adverse impact on our business and financial condition.

We have not previously submitted an NDA to the FDA, or similar drug approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any future product candidates will be successful in clinical trials or receive regulatory approval. Even though KORSUVA (CR845/difelikefalin) injection is in its Phase 3 clinical development for the treatment of dialysis patients with CKD-aP, it is, nonetheless, susceptible to the risks of failure inherent at any stage of product development, including the appearance of unexpected adverse events or failure to achieve its primary endpoints in these or subsequent clinical trials. Further, KORSUVA (CR845/difelikefalin) injection may not receive regulatory approval even if it is successful in clinical trials. If approved for marketing by applicable regulatory

authorities, our ability to generate revenues from KORSUVA (CR845/difelikefalin) injection will depend on our ability to:

- create market demand for KORSUVA (CR845/difelikefalin) injection through our own marketing and sales activities in the United States, and any other arrangements to promote this product candidate we may otherwise establish;
- hire, train and deploy a sales force to commercialize KORSUVA (CR845/difelikefalin) injection in the United States;
- manufacture KORSUVA (CR845/difelikefalin) injection in sufficient quantities and at acceptable quality and manufacturing cost to meet commercial demand at launch and thereafter;
- establish and maintain agreements with wholesalers, distributors and group purchasing organizations on commercially reasonable terms;
- maintain existing partnerships and/or create new partnerships with, or offer licenses to, third parties to promote and sell KORSUVA (CR845/difelikefalin) injection in foreign markets where we receive marketing approval;
- maintain patent and trade secret protection and regulatory exclusivity for KORSUVA (CR845/difelikefalin) injection;
- launch commercial sales of KORSUVA (CR845/difelikefalin) injection, whether alone or in collaboration with others;
- achieve market acceptance of KORSUVA (CR845/difelikefalin) injection by patients, the medical community and third-party payers;
- achieve coverage and adequate reimbursement from third-party payers for KORSUVA (CR845/difelikefalin) injection;
- effectively compete with other competing therapies; and
- maintain a continued acceptable safety profile of KORSUVA (CR845/difelikefalin) injection following launch.

As we continue to develop our other current or future product candidates, including Oral KORSUVA (CR845/difelikefalin), we expect to face similar risks to our ability to develop, obtain regulatory approval for and successfully commercialize such product candidates as we face with KORSUVA (CR845/difelikefalin) injection.

***CR845/difelikefalin acts as a selective kappa opioid receptor agonist, which is a drug class that has not previously yielded a successful commercial product for pruritus or pain indications.***

The development of product candidates based on peripheral kappa opioid receptor agonists is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates that work through this mechanism are relatively recent. The scientific evidence to support the feasibility of developing differentiated product candidates based on these discoveries is both preliminary and limited. We believe that we are among a relatively small group of companies that are pursuing the development of product candidates based on peripherally acting kappa opioid receptor agonists. In addition, we believe that companies that previously explored the development of kappa opioid receptor agonists abandoned these efforts because those prior generation kappa agonists, which were centrally active, resulted in psychiatric side effects. Although CR845/difelikefalin is a peripherally acting kappa opioid receptor agonist and these side effects have not been observed in any of our clinical trials to date, it is

possible that we could observe similar side effects, or other unacceptable adverse events. As a result, our approach to developing product candidates based on peripheral kappa opioid receptor agonists may not be successful and may never lead to marketable products.

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

Because we have limited financial and managerial resources, we focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently primarily focused on the development of KORSUVA (CR845/difelikefalin) injection for CKD-aP in hemodialysis patients and Oral KORSUVA (CR845/difelikefalin) for CKD-aP in pre-dialysis patients, CLD-aP and certain dermatological conditions, including AD. 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. 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 R&D programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

***Our future growth may depend on our ability to identify and develop products and if we do not successfully identify and develop product candidates or integrate them into our operations, we may have limited growth opportunities.***

A component of our business strategy is to continue to develop a pipeline of product candidates by developing products that we believe are a strategic fit with our focus on pain and pruritus therapeutics. However, these business activities may entail numerous operational and financial risks, including:

- difficulty or inability to secure financing to fund development activities for such development;
- disruption of our business and diversion of our management’s time and attention;
- higher than expected development costs;
- exposure to unknown liabilities;
- difficulty in managing multiple product development programs; and
- inability to successfully develop new products or clinical failure.

We have limited resources to identify and execute the development of products. Moreover, we may devote resources to potential development that are never completed, or we may fail to realize the anticipated benefits of such efforts. If we do not successfully develop and commercialize product candidates, we may not be able to obtain product revenues in future periods.

***The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired.***

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the

substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates, including KORSUVA (CR845/difelikefalin) injection and Oral KORSUVA (CR845/difelikefalin), or any product candidates we may seek to develop in the future, will ever obtain regulatory approval.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the European Medicines Agency, or EMA, and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing that product candidate. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs and consultants to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful. For example, the fact that we reported positive results from the double blinded phase of our KALM-1 trial of KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in patients undergoing hemodialysis does not mean that our ongoing Phase 3 efficacy and safety trials for KORSUVA (CR845/difelikefalin) injection will be completed successfully. We may also experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have to suspend clinical trials, as in the case of the IND clinical hold placed on our adaptive Phase 3 trial of I.V. CR845/difelikefalin for postoperative pain in February 2016, which was subsequently removed in April 2016, or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;

- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- changes in marketing approval policies during the development period;
- changes in or the enactment of additional statutes or regulations;
- changes in regulatory review for each submitted product application;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

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

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

Furthermore, regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies, including with respect to third-party technology used in any of our product candidates such as the excipient we intend to use for Oral KORSUVA (CR845/difelikefalin). 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.

Finally, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these scenarios could compromise the commercial prospects for our product candidates to assure safe use of the product candidates, either as a condition of product candidate approval or on the basis of new safety information.

If we experience delays in obtaining approval, if we fail to obtain approval of a product candidate or if the label for a product candidate does not include the labeling claims necessary or desirable for the successful commercialization

of that product candidate, the commercial prospects for such product candidate may be harmed and our ability to generate revenues will be materially impaired.

***We have been granted breakthrough therapy designation for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe pruritus associated with CKD in hemodialysis patients, however, it may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that KORSUVA (CR845/difelikefalin) injection will receive marketing approval.***

In June 2017, the FDA granted breakthrough therapy designation for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe uremic pruritus in CKD patients undergoing hemodialysis. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA may also be eligible for accelerated approval if the relevant criteria are met.

The receipt of a breakthrough therapy designation for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe uremic pruritus in CKD patients undergoing hemodialysis may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, the FDA may later decide that it no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

***The FDA may determine that I.V. CR845/difelikefalin, or any of our other current or future product candidates, has undesirable side effects that could limit dosage in development, delay or prevent their regulatory approval or commercialization.***

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to limit dosage in development or interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, in February 2016, the FDA placed our adaptive trial of I.V. CR845/difelikefalin for postoperative pain on IND clinical hold pending a safety review. The clinical hold was based on a stopping rule related to elevated serum sodium levels of greater than 150 mmol/L. After the safety review was completed, the FDA removed this clinical hold in April 2016 and the clinical trial was resumed in June 2016. If other concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical testing, the FDA may order us to cease further development, decline to approve the drug or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug. The number of such requests for additional data or information issued by the FDA in recent years has increased and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by I.V. CR845/difelikefalin or any of our other current or future product candidates could also result in denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications or the inclusion of unfavorable information in our product labeling, and in turn prevent us from commercializing and generating revenues from the sale of I.V. CR845/difelikefalin or any other product candidate.

To date, the side effects observed in the completed I.V. CR845/difelikefalin clinical trials include dizziness, transient facial tingling, a state of near-sleep, or somnolence, and hypernatremia, an electrolyte disturbance that is defined by an elevated sodium level in the blood, which we believe is secondary, at least in part, to another side effect, aquaresis, that is defined as electrolyte-free urination. As described above, the observation of mild to moderate hypernatremia in our adaptive trial for postoperative pain triggered a stopping rule in the trial protocol and led the FDA to institute an IND clinical hold related to the trial, pending a safety review. Prolonged aquaresis can result in a negative fluid balance if the excreted water is not replaced by oral or intravenous fluids, and although we recommend steps to control fluid balance, we cannot be certain that such instructions will be followed by healthcare providers and/or patients, and failure to follow such instructions may be accompanied by adverse events associated with negative fluid

balance, including disability and death. We believe that one such adverse event, which has been observed, postural tachycardia, an elevation of heart rate upon standing up, is a physiological reflex that can be triggered as a result of decreased intravascular volume caused by a negative fluid balance. We have observed transient prolactin elevations, which are brief increases in the concentration of the hormone prolactin in the bloodstream, in response to I.V. CR845/difelikefalin, which we have measured as a nonselective opioid biomarker since both kappa and mu opioids elicit this effect. We cannot be certain that such elevations in prolactin will be transient, safe, and well tolerated in all patients. In addition, previously developed kappa opioid agonists, the pharmacological class of drugs that CR845/difelikefalin belongs to, have been associated with poorly tolerated psychiatric side effects, such as a feeling of emotional and mental discomfort, or dysphoria, and hallucinations, at high doses, particularly for prior generations of kappa opioid agonists with substantially unrestricted or only partially restricted entry to the CNS. Although we have not observed psychiatric side effects in any CR845/difelikefalin clinical trials to date, we cannot be certain that these side effects or others will not be observed 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. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

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

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

***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 conducting clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the eligibility criteria for, and design of, the trial in question;
- the perceived risks and benefits of the product candidate under study;
- competition in recruiting and enrolling patients in clinical trials;

- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. We may encounter difficulties and/or delays in completing our planned enrollments. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, or the inability to complete development of our product candidates, which would cause the value of our company to decline, limit our ability to obtain additional financing, and materially impair our ability to generate revenues.

***CR845/difelikefalin is a kappa opioid receptor agonist and, if approved, will exist in the marketplace with mu opioid products that are subject to restrictive marketing and distribution regulations, which if applied to our product candidates would restrict their use and harm our ability to generate profits.***

Many currently approved mu opioid receptor agonists require 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 CR845/difelikefalin has been well tolerated in clinical trials to date and has not shown any evidence of the euphoria that has led to misuse, abuse and addiction of mu opioids, including the results of our Human Abuse Liability, or HAL, trial, which we successfully completed in the fourth quarter of 2014, the FDA may still determine that CR845/difelikefalin-based products require a REMS program, including for its use in non-pain indications such as KORSUVA (CR845/difelikefalin) injection for CKD-aP in hemodialysis patients or Oral KORSUVA (CR845/difelikefalin) for CKD-aP in pre-dialysis patients and CLD-aP. We cannot predict whether REMS will be required as part of the FDA's approval of our product candidates and, if required, what those requirements might be. Any limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of our product candidates, 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 these product candidates. Furthermore, risks of our product candidates that are not adequately addressed through proposed REMS for such product candidates may also prevent or delay their approval for commercialization.

In addition, currently approved mu opioids with which CR845/difelikefalin -based products may compete are controlled substances, which are subject to state, federal and foreign laws and regulations regarding their manufacture, use, sale, importation, exportation and distribution. Controlled substances are regulated under the federal Controlled Substances Act of 1970 and regulations of the DEA. The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances.

The results from our HAL trial suggest that CR845/difelikefalin may have the potential to be a Schedule V or non-scheduled peripheral opioid. However, while CR845/difelikefalin-based products have not demonstrated any evidence of the euphoria that has led to misuse, abuse, and addiction of mu opioids, and while CR845/difelikefalin-based products are not being treated as a controlled substance in clinical trials, it is possible that the DEA could determine that CR845/difelikefalin-based products should be regulated as controlled substances. Even if the DEA does not regulate CR845/difelikefalin-based products, including KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in hemodialysis patients and Oral KORSUVA (CR845/difelikefalin) for other pruritic conditions such as CKD-aP in pre-dialysis patients and CLD-aP, as controlled substances, public perception surrounding opioids as a class may lead to

public opposition to approvability of CR845/difelikefalin and limit its commercial potential. The ‘opioid crisis’ currently discussed among federal, state and local policymakers fails to distinguish between mu opioids and other opioids.

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

If any of our product candidates are classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors would be required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. Also, if any of our product candidates were classified as controlled substances, there is a risk that DEA regulations could limit the supply of the compounds used in clinical trials and, in the future, the ability to produce and distribute our products in the volume needed to meet 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. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of the restrictive nature of these regulations, if it were determined that our product candidates are subject to these restrictions, the commercialization of our product candidates could be limited.

***We will need to obtain FDA approval of any proposed product names, and any failure or delay associated with such approval may adversely affect our business.***

We have received conditional approval from the FDA for the use of KORSUVA as the proprietary name for our product candidate I.V. CR845/difelikefalin for the treatment of itch or pruritus. However, this approval is conditional upon a further and final review by the FDA at the time of NDA approval. Additionally, any name we intend to use for our other current or future product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the USPTO. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims or contributes to an overstatement of efficacy. If the FDA objects to any of our proposed product names, we may be required to adopt alternative names for our product candidates. If we adopt alternative names, we would lose any goodwill or brand recognition developed for the KORSUVA mark as well as the benefit of our existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

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

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

***Regulatory approval is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may be subject to fines, penalties or injunctions if we are determined to be promoting the use of our products for unapproved or "off-label" uses, resulting in damage to our reputation and business.***

When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific indications for which a product is approved. If we are not able to obtain FDA approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications that are not specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by pharmaceutical companies on off-label use. If the FDA determines that our promotional activities constitute promotion of an off-label use, it could request that we modify our promotional materials or subject us to regulatory or enforcement actions by other agencies, including issuance of warning letters or untitled letters, suspension or withdraw an approved product from the market, mandatory or voluntary recalls, civil fines, disgorgement of money, operating restrictions, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, injunctions or criminal prosecution, any of which could significantly harm our business.

***Even if one of our CR845/difelikefalin-based product candidates receives regulatory approval, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.***

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, will be subject to extensive and 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, continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and cGCPs for any clinical trials that we conduct post-approval. Even if marketing approval of a product candidate is granted, the approval may be subject to

limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including any requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

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

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

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

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

**Risks Related to the Commercialization of Our Product Candidates**

***We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies and other research organizations. Our operating results will suffer if we fail to compete effectively.***

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of pain and pruritus. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

There are a large number of companies developing or marketing therapies for the treatment and management of pruritus, including many major pharmaceutical and biotechnology companies. Among the companies that currently market or are developing therapies that, if approved, our product candidates may potentially compete with include: Pfizer, Menlo Therapeutics, Trevi, Vanda, Tioga, Leo Pharma, Chugai and others. Additionally, the market for the prevention and treatment of PONV is highly fragmented. There are a number of different agents alone or in combination (particularly in patients with a high risk for PONV) with different mechanism of actions to try to manage PONV. If approved, I.V. CR845/difelikefalin would likely be competing within the overall PONV market, although we expect that it would primarily be utilized as an add-on therapy in patients with a higher risk of PONV. Although most of the PONV products are generically available, there is still a significant segment of high-risk patients where their PONV is not adequately managed, which can increase the hospital length of stay and add significant cost to managing a post-operative patient.

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

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in R&D, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

***If we are unable to establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if they are approved, we may be unable to generate product revenues.***

We currently do not have a commercial infrastructure for the marketing, sale and distribution of pharmaceutical products. If approved, in order to commercialize our products, we must build our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. If KORSUVA (CR845/difelikefalin) injection is approved by the FDA, we plan to build a commercial infrastructure,

including our own specialty sales force, to launch KORSUVA (CR845/difelikefalin) injection in the hemodialysis setting in the United States. We may seek to further penetrate the U.S. market in the future by expanding our sales force or through collaborations with other pharmaceutical or biotechnology companies or third-party manufacturing and sales organizations. If approved for marketing outside the United States, our existing or new partners will commercialize KORSUVA (CR845/difelikefalin) injection outside the United States with their own, or their collaborators', sales force.

We have no prior experience in the marketing, sale and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure. The establishment and development of our own sales force and related compliance plans to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We, or our partners or collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage and retain marketing and sales personnel. In the event that we are unable to develop a marketing and sales infrastructure, we may not be able to commercialize KORSUVA (CR845/difelikefalin) injection or any of our other current or future product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our or our partners' or collaborators' efforts to commercialize KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates include:

- inability to recruit, train, manage and retain adequate numbers of effective sales and marketing personnel;
- inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates;
- inability to effectively oversee a geographically dispersed sales and marketing team;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

Although our current plan is to hire most of our sales and marketing personnel only if KORSUVA (CR845/difelikefalin) injection is approved by the FDA, we will incur expenses prior to product launch in recruiting this sales force and developing a marketing and sales infrastructure. If the commercial launch of KORSUVA (CR845/difelikefalin) injection is delayed as a result of FDA requirements or other reasons, we would incur these expenses prior to being able to realize any revenue from sales of KORSUVA (CR845/difelikefalin) injection. Even if we are able to effectively hire a sales force and develop a marketing and sales infrastructure, our sales force and marketing teams may not be successful in commercializing KORSUVA (CR845/difelikefalin) injection or any of our other current or future product candidates.

In the event that we are unable to collaborate with a third-party marketing and sales organization to commercialize any approved product candidates outside the United States, our ability to generate product revenues may be limited. To the extent that we rely on third parties to commercialize any products for which we obtain regulatory approval, we may receive less revenues than if we commercialized these products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts.

***To the extent that any of our product candidates, if approved, does not achieve broad market acceptance, the revenues that we generate from its sales will be limited.***

We have never commercialized a product candidate for any indication. Even if KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any of our other current or future product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may not gain acceptance among physicians, hospitals, dialysis providers, patients and third-party payers. If any product candidates for which we obtain regulatory approval do not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) and any

future product candidate by physicians, hospitals, dialysis providers, patients and third-party payers will depend on a number of factors, some of which are beyond our control. The degree of market acceptance of any of our product candidates will depend on a number of factors, including:

- the prevalence and severity of adverse events associated with such product candidate;
- limitations or warnings contained in the product's FDA-approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other pain management or pruritus products;
- changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following FDA approval, if obtained;
- the relative convenience and ease of administration of such product candidate;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;
- the availability of coverage and adequate reimbursement by third-party payers, such as insurance companies and other healthcare payers, and by government healthcare programs, including Medicare and Medicaid;
- the extent and strength of our marketing and distribution of such product candidate;
- the safety, efficacy and other potential advantages over, and availability of, alternative treatments already used to treat acute pain, chronic pain and/or pruritus;
- distribution and use restrictions imposed by the FDA with respect to such product candidate or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan;
- the timing of market introduction of such product candidate, as well as competitive products;
- our ability to offer such product candidate for sale at competitive prices;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; and
- the clinical indications for such product candidate if approved.

Our ability to effectively promote and sell KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) and any future product candidates, if approved, will also depend on pricing and cost effectiveness, including our ability to produce a product at a competitive price and achieve acceptance of the product onto dialysis organization or hospital formularies, and our ability to obtain sufficient third-party coverage or reimbursement. Generally, before we can attempt to sell CR845/difelikefalin injection in a hospital or dialysis provider, CR845/difelikefalin injection must be approved for addition to that institution's list of drugs approved for use in that institution, or formulary list. In evaluating drugs for inclusion on the formulary list, hospitals and dialysis providers evaluate a variety of factors, including cost. The frequency with which hospitals and dialysis providers add and remove drugs from their formulary lists varies from organization to organization, and institutions often require additional information prior to adding new drugs to their formulary, which may result in substantial delays in our receiving formulary approval for CR845/difelikefalin injection. Since most hospitals are members of group purchasing organizations, which leverage the purchasing power of a group of entities to obtain discounts based on the collective buying power of the group, our ability to attract customers in the hospital marketplace will also depend on our ability to effectively promote our product candidates to group purchasing organizations. We will also need to demonstrate acceptable evidence of safety and efficacy, as well as relative convenience and ease of administration. Market

acceptance could be limited depending on the prevalence and severity of any expected or unexpected adverse side effects associated with our product candidates.

Our efforts to educate the medical community and third-party payers on the benefits of our product candidates may require significant resources and may never be successful. Even if the medical community accepts that one of our product candidates is safe and effective for its approved indications, physicians and patients may not immediately be receptive to such product candidate and may be slow to adopt it as an accepted treatment of pain or pruritus. It is unlikely that any labeling approved by the FDA will contain claims that one of our product candidates is safer or more effective than competitive products or will permit us to promote such product candidate as being superior to competing products. Further, the availability of inexpensive generic forms of products for acute and chronic pain as well as pruritus may also limit acceptance of our product candidates among physicians, patients and third-party payers. If KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any future product candidate, is approved but does not achieve an adequate level of acceptance among physicians, patients and third-party payers, we may not generate meaningful revenues from KORSUVA (CR845/difelikefalin) injection, Oral CR845/difelikefalin or such other product candidate, and we may not become profitable.

***We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for KORSUVA (CR845/difelikefalin) injection or other product candidates that we may develop and may have to limit their commercialization.***

The use of KORSUVA (CR845/difelikefalin) injection or Oral KORSUVA (CR845/difelikefalin) and any future product candidate in clinical trials and the sale of any products for which we obtain regulatory approval expose us to the risk of product liability claims. We face inherent risk of product liability related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Product liability claims might be brought against us by consumers, healthcare providers or others using, administering or selling our products. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- loss of revenue from decreased demand for our products and/or product candidates;
- impairment of our business reputation or financial stability;
- costs of related litigation;
- substantial monetary awards to patients or other claimants;
- diversion of management attention;
- withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs;
- the inability to commercialize our product candidates;
- significant negative media attention;
- initiation of investigations by regulators; and
- product recalls, withdrawals or labeling, marketing or promotional restrictions.

We have obtained limited product liability insurance coverage for our products and our clinical trials with a $10.0 million annual aggregate coverage limit in the United States and various other coverage limits outside of the United States. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage to include the sale of commercial products if we obtain FDA approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

**Risks Related to Our Dependence on Third Parties**

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

We rely on third-party CROs to conduct our preclinical and clinical trials for all of our product candidates, and do not plan to independently conduct clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our preclinical studies and clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities and adversely affect our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with GLP, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Our CROs may also have relationships with other entities, some of which may be our competitors. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on-going clinical, non-clinical and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product

candidates. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

***If the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.***

We do not manufacture any of our product candidates, and we do not currently plan to develop any capacity to do so. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. It is our intention that by the time of any regulatory approvals for commercialization, we will have negotiated long-term commitments with at least one primary supplier for each manufacturing and distribution function, and in July 2019, we entered into a non-exclusive commercial manufacturing agreement with Patheon for KORSUVA (CR845/difelikefalin) injection. Any problems or delays we experience in preparing for commercial-scale manufacturing of a product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities, which would adversely affect our business. For example, our manufacturers will need to produce specific batches of our product candidates to demonstrate acceptable stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities this acceptable stability data for our product candidates, as well as validate methods and manufacturing processes, in order to receive regulatory approval to commercialize KORSUVA (CR845/difelikefalin) injection or any other product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide product candidates to patients in our clinical trials would be jeopardized.

Further, we may rely on proprietary technology developed by our contract manufacturers for purposes of manufacturing certain of our product candidates and our failure to negotiate or maintain the long-term use of any such proprietary technology or the inability for our contract manufacturers to produce our product candidates or components of our product candidates in the volumes that we require on a timely basis, may lead to delays or interruptions in the regulatory approval or commercialization process, as well as increased costs. For example, in August 2019, we entered into the Enteris License Agreement and intend to use Enteris's Peptelligence® technology to develop, manufacture and commercialize Oral KORSUVA (CR845/difelikefalin). If we experience any interruptions in the manufacture, delivery or scale-up of the Enteris formulation technology, including as a result of factors that may be outside of their control such as the recent coronavirus outbreak, we may experience delays in the development and commercialization of Oral KORSUVA (CR845/difelikefalin). Further, if we are unable to maintain our relationship with Enteris, we may be forced to reformulate Oral KORSUVA (CR845/difelikefalin) which could result in significantly delaying commercializing Oral KORSUVA (CR845/difelikefalin) and require us to incur additional costs in connection with such reformulation and potentially needed to seek additional approvals from the FDA.

In addition, all manufacturers of our product candidates must comply with cGMP requirements enforced by the FDA through its facilities inspection program. These requirements include quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. We have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension, delay or denial of product approval, product seizure or recall, or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our product candidates.

***We may rely on third parties to perform many essential services for any products that we commercialize, including services related to warehousing and inventory control, distribution, customer service, accounts receivable management, cash collection and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize I.V. CR845/difelikefalin or any other product candidate, will be significantly impacted and we may be subject to regulatory sanctions.***

We may retain third-party service providers to perform a variety of functions related to the sale and distribution of KORSUVA (CR845/difelikefalin) injection and our other current or future product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to warehousing and inventory control, distribution, customer service, accounts receivable management and cash collection, and, as a result, most of our inventory may be stored at a single warehouse maintained by one such service provider. If we retain this provider, we would substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired. In addition, we may engage third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

***We are dependent on our collaboration agreements for certain revenues, and if our commercial partners do not perform their obligations under such agreements, we could lose revenues.***

In May 2018, we entered into an agreement with VFMCRP under which we granted VFMCRP a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients worldwide (excluding the United States, Japan and South Korea). In April 2013, we entered into an agreement with Maruishi under which we granted Maruishi an exclusive license to develop, manufacture and commercialize products containing CR845/difelikefalin in Japan. Also, in April 2012, we entered into an agreement with CKDP under which we granted CKDP an exclusive license to develop, manufacture and commercialize products containing CR845/difelikefalin in South Korea. Under the VFMCRP Agreement, we are responsible, at our own cost, to undertake clinical and non-clinical development. We are also responsible to provide all content and subject matter expertise required for registration with the EMA in the EU that will be needed by VFMCRP for such registration, including participation in regulatory meetings, as needed. If third-party costs incurred by us with respect to our clinical development for the EMA registration exceed $20,000, such excess costs will be shared equally by us and VFMCRP. VFMCRP will contribute, at its own cost, its clinical development expertise as reasonably useful for such development activities, such as preparing the clinical results that we present to it in a

format acceptable to the EMA to obtain marketing approval in the EU. Maruishi and CKDP are required to use commercially reasonable efforts, at their expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in Japan and South Korea, respectively. Our receipt of milestone payments and royalties under these agreements is dependent on the continued efforts by VFMCRP, Maruishi and CKDP, respectively, and their failure to adequately develop or commercialize the licensed products, or any default or inability to meet their payment obligations under their respective agreements, could harm our revenues and business.

***Any collaboration arrangements that we are a party to or may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.***

Our business model is to commercialize our product candidates in the United States and generally to seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our product candidates in the rest of the world. We currently have license agreements with VFMCRP (I.V. CR845/difelikefalin for CKD-aP in dialysis patients) as well as Maruishi and CKDP (CR845/difelikefalin – both I.V. and Oral). In addition to our existing agreements, we may enter into additional collaboration arrangements in the future on a selective basis. Our existing collaborations and future collaboration arrangements may not be successful. The success of our existing and future collaboration arrangements will depend heavily on the efforts and activities of our collaborators.

Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaboration arrangements. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority.

Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. For example, the VFMCRP, Maruishi and CKDP Agreements may be terminated by our collaborator for our breach or insolvency, VFMCRP may terminate its agreement (in its entirety or with respect to any countries within the Territory upon written notice to us) upon the earlier of (1) acceptance for filing of an NDA covering Licensed Product filed with the FDA (after completion of the Phase 3 program) or (2) the third anniversary of the Effective Date. Maruishi may terminate its agreement with us at will, and CKDP may terminate its agreement with us in certain circumstances relating to patent invalidity or unenforceability or generic entry by a third party, as further described in the section titled “Business — Commercial Partnerships” above. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Our current collaborations and any future collaborations we might enter into may pose a number of risks, including the following:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval 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, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

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

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

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

- collaborations, including our collaboration with Maruishi, may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our current collaborations or any other collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. All of the risks relating to our product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of our collaborators in their respective jurisdictions.

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

For KORSUVA (CR845/difelikefalin) injection and any other current or future product candidates, we may in the future determine to collaborate with additional pharmaceutical and biotechnology companies for their development and potential commercialization. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator’s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator’s evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization

activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

***We are dependent on third parties to decide to utilize KORSUVA (CR845/difelikefalin) injection and to make it readily available at the point of care throughout their dialysis centers or hospitals.***

In addition to extensive internal efforts, the successful commercialization of KORSUVA (CR845/difelikefalin) injection will require many third parties, over whom we have no control, to decide to utilize KORSUVA (CR845/difelikefalin) injection and to make it readily available at the point of care throughout their hospitals. These third parties include physicians, dialysis providers, pharmacists and hospital pharmacy and therapeutics committees, which are commonly referred to as P&T committees. Generally, even if CR845/difelikefalin injection is approved by the FDA, before we can attempt to sell CR845/difelikefalin injection in a hospital or dialysis center, CR845/difelikefalin injection must be approved for addition to that hospital or dialysis center's list of approved drugs, or formulary list, by the institution's P&T committee. An institutional P&T committee typically governs all matters pertaining to the use of medications within the institution, including review of medication formulary data and recommendations for the appropriate use of drugs within the institution to the medical staff. The frequency of P&T committee meetings at various institutions varies considerably, and P&T committees often require additional information to aid in their decision-making process, so we may experience substantial delays in obtaining formulary approvals. Additionally, institutions may be concerned that the cost of acquiring CR845/difelikefalin injection for use in their institutions will adversely impact their overall pharmacy budgets, which could cause institution staff to resist efforts to add CR845/difelikefalin injection to the formulary, or to implement restrictions on the usage of the drug in order to control costs, either initially or later, when the increasing use of CR845/difelikefalin injection within their institution begins to significantly impact their budgets. We cannot guarantee that we will be successful in getting the approvals we need from enough P&T committees and overcoming any financial objections raised by institution staff quickly enough to maintain and grow institutional sales of CR845/difelikefalin injection.

**Risks Related to Legal and Compliance Matters**

***If we fail to comply with federal and state healthcare laws, including fraud and abuse, transparency and health information laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected.***

As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payers, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, transparency and patients' rights may be applicable to our business. The healthcare laws and regulations that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which regulates, among other things, our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, any person or entity from knowingly and willfully soliciting, receiving, offering or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, recommendation, lease, order or furnishing of an item or service reimbursable, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws, including without limitation the federal civil False Claims Act, and civil monetary penalties law, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment or approval from a federal health care program (including Medicare and Medicaid);

- HIPAA, which created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to

obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program, regardless of the payer (e.g., public or private) and knowingly and willfully falsifying, concealing, or covering up by any trick, scheme or device a material fact or making any materially false statements in connection with the delivery of, or payment for, health care benefits, items or services relating to healthcare matters;

- federal transparency laws, including the federal Physician Payments Sunshine Act, that 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 to report annually to CMS, or Centers for Medicare & Medicaid Services, information related to payments and other transfers of value provided to physicians, as defined by such law, and teaching hospitals, and applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to the pricing of certain drugs, as well as payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and local laws that require the registration of pharmaceutical sales representatives, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under these laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Pharmaceutical and other healthcare companies continue to be prosecuted under the federal false claims laws for numerous activities, including those related to research, sales, marketing and promotional programs. In addition, recent health care reform legislation has strengthened these laws. For example, the Health Care Reform Law among other things, amends the intent requirement of the federal Anti-Kickback Statute and certain other criminal healthcare fraud statutes. As a result, a person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to commit a violation. Moreover, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. To the extent that any product we make is sold in a foreign country, we may be subject to similar foreign laws and regulations. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, exclusion from participation in U.S. federal or state health care programs, contractual damages, reputational harm, imprisonment, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state transparency and fraud and abuse laws may prove costly. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to significant criminal, civil or administrative sanctions, including but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business.

***Changes in and failures to comply with applicable U.S. and foreign privacy and data protection laws, regulations and standards may subject us to liabilities and adversely affect our business, operations and financial performance.***

We are subject to or affected by numerous federal, state and foreign laws and regulations, as well as regulatory guidance, governing the collection, use, disclosure, retention, and security of personal data, such as information that we collect about participants and healthcare providers in connection with clinical trials in the U.S. and abroad. The global data protection landscape is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution may create uncertainty in our business, affect our or our service providers' ability to operate in certain jurisdictions or to collect, store, transfer use and share personal data, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state, or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising.

In the U.S., HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, including health plans, healthcare clearinghouses, certain healthcare providers, and their business associates that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information. In the event we are subject to HIPAA and fail to properly maintain the privacy and security of certain individually identifiable health information, or we are responsible for an inadvertent disclosure or security breach of such individually identifiable health information, we could be subject to enforcement measures, including civil and criminal penalties and fines for violations of state and federal privacy or security standards, such as HIPAA and HITECH, and their respective implementing regulations. Additionally, certain states have adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. On June 28, 2018, California enacted the California Consumer Privacy Act, or CCPA, which takes effect on January 1, 2020. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. Many countries in these regions have established or are in the process of establishing privacy and data security legal frameworks with which we or our partners, collaborators, customers, or service providers must comply. For example, the EU has adopted the General Data Protection Regulation, or GDPR, which went into effect in May 2018 and introduced strict requirements for processing personal data. The GDPR is likely to increase compliance burden on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and leverage information about them or how we obtain consent from them. The processing of sensitive personal data, such as physical health condition, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators and supervisory bodies involved in the review and approval of clinical trials. In addition, the GDPR provides for breach reporting requirements, more robust regulatory enforcement and fines of up to 20 million euros or up to 4% of the annual global revenue. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

U.S. and foreign data protection laws, regulations and standards are subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. Any liability from failure to comply with the requirements of these laws, to the extent such requirements are deemed to apply to our operations, could adversely affect our financial condition. The costs of

complying with privacy and security related legal and regulatory requirements are burdensome and could have a material adverse effect on our results of operations.

***If the government or other third-party payers fail to provide coverage and adequate reimbursement and payment rates for KORSUVA (CR845/difelikefalin) injection or any of our other current or future product candidates, if any, or if providers choose to use therapies that are less expensive, our revenue and prospects for profitability will be limited.***

In both domestic and foreign markets, sales of our future products will depend in part upon the availability of coverage and reimbursement from third-party payers. Such third-party payers include government health programs such as Medicare and Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. KORSUVA (CR845/difelikefalin) injection for the treatment of pruritus in hemodialysis patients may be designated as a component of the government's bundled reimbursement for end stage renal disease treatment.

On October 31, 2019, CMS issued a final rule that revises payment policies and rates under the End-Stage Renal Disease Prospective Payment System, or ESRD PPS, for renal dialysis services furnished to beneficiaries on or after January 1, 2020. The final rule also updates the Transitional Drug Add-On Payment Adjustment, or TDAPA. In the final rule, CMS revised ESRD PPS eligibility to focus on innovative drugs and excluded certain drugs from being eligible for the TDAPA. CMS will pay the revised TDAPA adjustment, which is called the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies , or TPNIES, for equipment and supplies that: (1) have been designated by CMS as a renal dialysis service, (2) are new, meaning granted marketing authorization by FDA on or after January 1, 2020, (3) are commercially available by January 1 of the particular calendar year, meaning the year in which the payment adjustment would take effect, (4) have a Healthcare Common Procedure Coding System, or HCPCS, application submitted in accordance with the official Level II HCPCS coding procedures by September 1 of the particular calendar year, (5) are innovative, meaning they meet the substantial clinical improvement criteria specified in the Inpatient Prospective Payment System regulations and related guidance, and (6) are not capital-related assets. Based on this ruling, we expect KORSUVA (CR845/difelikefalin) injection, if approved for CKD-aP in hemodialysis patients, will qualify for TDAPA payments for two years post approval. However, there is no assurance that KORSUVA (CR845/difelikefalin) injection will qualify for TDAPA payments or, even if it does, that it will be able to maintain its price established in the TDAPA period in the post-TDAPA timeframe.

Additionally, many U.S. hospitals receive a fixed reimbursement amount per procedure for certain surgeries and other treatment therapies they perform, or a pre-determined rate for all hospital inpatient care provided as payment in full. Because, in these instances, the amount of reimbursement that such providers receive may not be based on the actual expenses the provider incurs, providers may choose to use therapies which are less expensive when compared to our product candidates. Accordingly, KORSUVA (CR845/difelikefalin) injection or any of our other current or future product candidates, if approved, will face competition from other therapies and drugs for these limited provider financial resources. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of hospitals, other target customers and their third-party payers. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Third-party coverage and adequate reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payers. Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, results of operations, financial condition and prospects.

***We are subject to recent legislation, regulatory proposals and healthcare payer initiatives that may increase our costs of compliance and adversely affect our ability to market our products, obtain collaborators and raise capital.***

In March 2010, President Obama signed the Health Care Reform Law, which includes provisions that have changed, and likely will continue to change, health care financing and the delivery of health care in the United States. Among the provisions of the Health Care Reform Law of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively;
- 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;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new transparency requirements under the federal Physician Payments Sunshine Act;
- a new requirement to annually report certain drug samples that manufacturers and distributors provide to licensed practitioners, or to pharmacies of hospitals or other healthcare entities;
- a licensure framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- establishment of a Center for Medicare & Medicaid Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending; and
- expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance.

There remain judicial and Congressional challenges to certain aspects of the Health Care Reform Law, as well as efforts by the Trump administration to repeal or replace certain aspects of the Health Care Reform Law. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the

implementation of certain provisions of the Health Care Reform Law or otherwise circumvent some of the requirements for health insurance mandated by the Health Care Reform Law. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Health Care Reform Law. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Health Care Reform Law have been signed into law. The TCJA includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Health Care Reform Law on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". In addition, the 2020 federal spending package permanently eliminates, effective January 1, 2020, the Health Care Reform Law's 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. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Health Care Reform Law, effective January 1, 2019, to close the coverage gap in most Medicare drug plans. In December 2018, CMS published a new final rule permitting further collections and payments to and from certain Health Care Reform Law qualified health plans and health insurance issuers under the Health Care Reform Law risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Health Care Reform Law is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the TCJA. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the Health Care Reform Law are invalid as well. It is unclear how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the Health Care Reform Law will impact the Health Care Reform Law and our business.

In addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. These changes include, among other things, aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went effective on April 1, 2013 and, following passage of the Bipartisan Budget Act of 2015, and subsequent legislative amendments, including the BBA, will remain in effect until 2029, 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 and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

We expect that the Health Care Reform Law, as well as other federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payers. In addition, 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 cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2020 contains additional drug price control measures that could be enacted during the budget process or in other future legislation, such as 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. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services, or HHS, has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented 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, to encourage importation from other countries and bulk purchasing. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. Moreover, the Drug Supply Chain Security Act imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing.

Legislation and regulations that, among other things, reduce drug prices or require the implementation of costly compliance measures could result in decreased net revenues from our pharmaceutical products and decrease potential returns from our development efforts, and we cannot predict what legislation will be enacted in the future.

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

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payers, that an adequate level of reimbursement will be available or that the third-party payers' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

***Our employees, independent contractors, consultants, and commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.***

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants and commercial partners. Misconduct by such individuals could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, report financial information or data accurately or disclose unauthorized activities to us. Third party misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

***Our business involves the use of hazardous materials and we must comply with environmental laws and regulations, which can be expensive and restrict how we do business.***

Our manufacturing activities involve the controlled storage, use and disposal of hazardous materials, including the components of our products, product candidates and other hazardous compounds. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling, release and disposal of, and exposure to, these hazardous materials. Violation of these laws and regulations could lead to substantial fines and penalties. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

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

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

**Risks Related to Intellectual Property**

***It is difficult and costly to protect our proprietary rights and as a result we may not be able to ensure their protection and all patents will eventually expire.***

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection for CR845/difelikefalin and for any other product candidates that we may develop, license or acquire and the methods we use to manufacture them, as well as successfully defending these patents and trade secrets against third-party challenges. We will only be able to protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute to issuance all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our R&D output before it is too late to obtain patent protection. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be successfully prosecuted to issuance and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. The degree of future protection for our proprietary rights is uncertain, because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting CR845/difelikefalin and any other product candidates that we may develop, license or acquire by obtaining and defending patents. For example:

- we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents;

- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;
- the issued patents covering our product candidates may not provide a basis for commercially viable active products, may not provide us with any competitive advantages, or may be challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- noncompliance with governmental patent agencies requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office has developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, including and in particular, the first to file provisions, became effective on March 16, 2013. The Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our currently pending and future patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Patent applications in the United States are generally maintained in confidence for at least 18 months after their earliest effective filing date and in certain circumstances not until granted when no foreign counterpart patent applications are filed. Furthermore, published patent applications may issue at a later date with new and/or amended claims substantially different from those published earlier. Consequently, we cannot be certain we were the first to invent or the first to file patent applications on CR845/difelikefalin or any other product candidates that we may develop, license or acquire.

Until recent changes to the U.S. Patent Laws, patents and patent applications relating to substantially similar claimed inventions were potentially subject to interference proceedings to determine the first applicant to invent the claimed subject matter. For an interference to be declared against Cara’s patents and patent applications, any such interference would be under the 1952 law which was eliminated by the America Invents Act, or AIA, enacted in 2011 and fully effective in 2013. Such an interference would therefore have to relate to a patent or application with an effective filing date before March 16, 2013. No interference with such a patent or application has been declared to date. Therefore, it seems extremely unlikely that we may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office to determine priority of invention in the United States against one or more parties claiming the same or similar invention. However, in the unlikely event that such interference was to be declared, the

costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U.S. patent position. The results of these types of proceedings could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such results could have a material adverse effect on our results of operations.

In addition, the patentability of claims in pending patent applications covering a CR845/difelikefalin-based product can be challenged by third parties during prosecution in the U.S. Patent and Trademark Office under the new AIA law of 2013, for example by third party observations and derivation proceedings, and the validity of claims in issued patents can be challenged by third parties in various post-grant proceedings such as Post-Grant Review, Inter-partes Reexamination, and Inter-partes Review proceedings.

Furthermore, we may not have identified all United States and foreign patents or published applications that affect our business either by blocking our ability to commercialize our drugs or by covering similar technologies that affect our drug market. In addition, some countries, including many in Europe, do not grant patent claims directed to methods of treating humans, and in these countries patent protection may not be available at all to protect our product candidates. Even if patents issue, we cannot guarantee that the claims of those patents will be valid and enforceable or provide us with any significant protection against competitive products, or otherwise be commercially valuable to us.

We also rely on trade secrets to protect our technology, particularly where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our licensors, employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

If we fail to obtain or maintain patent protection or trade secret protection for CR845/difelikefalin or any other product candidate that we may develop, license or acquire, third parties could use our proprietary information, which could impair our ability to compete in the market and adversely affect our ability to generate revenues and achieve profitability.

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

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

***If we or any current or future collaboration partner are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any litigation would harm our business.***

Our ability to develop, manufacture, market and sell KORSUVA (CR845/difelikefalin) injection or any of our other current of future product candidates depends upon our ability to avoid infringing the proprietary rights of third

parties, and our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the general field of pain management and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our results of operations. Regardless of the outcome of any litigation, defending the litigation may be expensive, time-consuming and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates may infringe. There could also be existing patents of which we are not aware that KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates may inadvertently infringe.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and biopharmaceutical industries generally. If a third-party claims that we infringe on their products or technology, we could face a number of issues, including:

- infringement and other intellectual property claims which, with or without merit, can be expensive and time consuming to litigate and can divert management's attention from our core business;
- substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor's patent;
- a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do;
- if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and
- redesigning our processes so they do not infringe, which may not be possible or could require substantial funds and time.

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

***We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and may ultimately be unsuccessful.***

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

in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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 this type of litigation.

Most of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

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

A third party may hold intellectual property, including patent rights that are important or necessary to the development or commercialization of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms or at all, which could materially harm our business.

***We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.***

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly 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. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

***The validity and enforceability of the patents and applications that cover our CR845/difelikefalin product candidates can be challenged by competitors.***

If KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any future product candidate is approved by the FDA, one or more third parties may challenge the patents covering these product candidates, which could result in the invalidation of, or render unenforceable, some or all of the relevant patent claims. For example, if a third party files an Abbreviated New Drug Application, or ANDA, for a generic drug product containing CR845/difelikefalin, and relies in whole or in part on studies conducted by or for us, the third party will be required to certify to the FDA that either: (1) there is no patent information listed in the FDA's Orange Book with respect to our NDA for KORSUVA (CR845/difelikefalin) injection; (2) the patents listed in the Orange Book have expired; (3) the listed patents have not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patents are invalid or will not be infringed by the manufacture, use or sale of the third-party's generic drug product. A certification that the new product will not infringe the Orange Book-listed patents for CR845/difelikefalin, or that such patents are invalid, is called a paragraph IV certification. If the third party submits a paragraph IV certification to the FDA, a notice of the paragraph IV certification must also be sent to us once the third-party's ANDA is accepted for filing by the FDA. We may then initiate a lawsuit to defend the patents identified in the notice. The filing of a patent infringement lawsuit within 45 days of receipt of the notice automatically prevents the FDA from approving the third-party's ANDA until the earliest of 30 months or the date on which the patent expires, the lawsuit is settled, or the court reaches a decision in the infringement lawsuit in favor of the third party. If we do not file a patent infringement lawsuit within the required 45-day period, the third-party's ANDA will not be subject to the 30-month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be very expensive and time-consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products.

**Risks Related to Employee Matters and Managing Growth**

***Our internal information technology systems, or those of our CROs, contract manufacturers or other contractors or consultants, may fail or suffer security breaches, loss or leakage of data and other disruptions, which could result in a material disruption of our development programs, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability, which could adversely affect our business.***

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party contractors who have access to our confidential information.

Despite the implementation of security measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third-party CROs, contract manufacturers and other contractors and consultants are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners and/or other third parties, or from cyber-attacks by malicious third parties (including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information), which may compromise our system infrastructure or lead to data leakage. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of our product candidates could be delayed.

While we have not experienced any such system failure, accident or security breach to date, we cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems or other cyber incidents that could adversely affect our business. For example, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs and the development and commercialization of CR845/difelikefalin injection, if approved, could be delayed. In addition, the loss of clinical trial data could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or security breaches could result in the loss, misappropriation and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could adversely affect our business.

***We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.***

As of February 24, 2020, we had 67 employees. We will need to substantially expand our managerial, commercial, financial, manufacturing and other personnel resources in order to manage our operations and prepare for the commercialization of CR845/difelikefalin injection, if approved. Our management and personnel systems and facilities currently in place may not be adequate to support this future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Our need to effectively manage our operations, growth and various projects requires that we:

- continue the hiring and training of an effective commercial organization in anticipation of the potential approval of KORSUVA (CR845/difelikefalin) injection, and establish appropriate systems, policies and infrastructure to support that organization;
- ensure that our consultants and other service providers successfully carry out their contractual obligations, provide high quality results, and meet expected deadlines;
- continue to carry out our own contractual obligations to our licensors and other third parties; and
- continue to improve our operational, financial and management controls, reporting systems and procedures.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

***We may not be able to manage our business effectively if we are unable to attract and retain key personnel.***

We may not be able to attract or retain qualified management and commercial, scientific and clinical personnel due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses. If we are not able to attract and retain necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the skills and leadership of our management team, including Derek Chalmers, our President and Chief

Executive Officer. Our senior management may terminate their employment with us at any time. If we lose one or more members of our senior management team, our ability to successfully implement our business strategy could be seriously harmed. Replacing these 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 regulatory 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 additional key personnel. We do not maintain "key person" insurance for any of our executives or other employees.

***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, as amended, the Sarbanes-Oxley Act of 2002 and the rules and regulations of The Nasdaq Global Market. Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to perform system and process evaluation and testing of our internal control over financial reporting to allow our management to report on the effectiveness of our internal control over financial reporting in this Form 10-K. In addition, effective December 31, 2019, we are no longer an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act. Accordingly, we are also required to have our independent registered public accounting firm issue an opinion on the effectiveness of our internal control over financial reporting on an annual basis.

During the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. Further, we may in the future discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Moreover, our internal controls over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are unable to assert that our internal control over financial reporting is effective, or if our independent registered public accounting firm is unable to express an opinion on the effectiveness of our internal control over financial reporting, investors could lose confidence in the reliability of our financial statements, the market price of our stock could decline and we could be subject to sanctions or investigations by The Nasdaq Global Market, the SEC or other regulatory authorities.

***We no longer qualify as an emerging growth company, effective as of December 31, 2019, and are required to comply with certain provisions of the Sarbanes-Oxley Act and we may no longer take advantage of reduced disclosure requirements.***

As of December 31, 2019, we are considered a large accelerated filer and, as a consequence, have lost our status as an emerging growth company. We are no longer permitted to take advantage of certain exemptions from various disclosure and reporting requirements that are applicable to emerging growth companies, including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in periodic reports and proxy statements, and exemptions from the requirements of holding a non-binding advisory vote on executive compensation. As a result, we expect to incur additional legal, accounting and other expenses and devote significant management attention as we implement additional corporate governance practices and seek to comply with these additional disclosure and reporting requirements. Compliance with these requirements for the first time may be more difficult and consume more resources than we anticipate.

**Risks Related to Ownership of Our Common Stock**

***The market price of our common stock has been, and is likely to continue to be, highly volatile, and you may not be able to resell your shares at or above the price you paid for them.***

Since our initial public offering in January 2014 and through February 24, 2020, our stock price has been volatile, trading at prices ranging from $4.26 to $28.50, and it is likely that the trading price of our common stock will continue to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- delays in the commencement, enrollment and ultimate completion of our clinical trials, including our ongoing Phase 3 clinical trials for KORSUVA (CR845/difelikefalin) injection for CKD-aP and our ongoing and planned trials for KORSUVA injection and Oral KORSUVA in other indications;
- any delay or refusal on the part of the FDA in approving an NDA for KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates;
- the commercial success of KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any future product candidates, if approved by the FDA;
- results of clinical trials of KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any future product candidate or those of our competitors;
- actual or anticipated variations in quarterly or annual operating results;
- failure to meet or exceed financial projections we provide to the public;
- failure to meet or exceed the estimates and projections of the investment community, including securities analysts;
- introduction of competitive products or technologies;
- changes or developments in laws or regulations applicable to our product candidates;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- general economic and market conditions and overall fluctuations in U.S. equity markets;
- developments concerning our sources of manufacturing supply, warehousing and inventory control;
- disputes or other developments relating to patents or other proprietary rights;
- additions or departures of key scientific or management personnel;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;

- announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- changes in the market valuations of companies similar to us;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures;
- changes in the structure of healthcare payment systems;
- general conditions or trends in our industry; and
- the other factors described in this "Risk Factors" section.

In addition, the stock market in general, and the market for small pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

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

***If equity research analysts cease to publish research or reports about us or if they publish unfavorable research or reports about us, our business or our market, our stock price and trading volume could decline.***

The trading market for our common stock is likely to be influenced by the research and reports that equity research analysts publish about us and our business. As a relatively newly public company, to date we have only limited equity research analyst coverage. Additionally, we do not have any control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

***Our quarterly operating results may fluctuate significantly.***

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- the successful progress of our clinical trials for KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) and other potential future product candidates;
- whether the FDA requires us to complete additional, unanticipated studies, tests or other activities prior to approving KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates, which would likely further delay any such approval;
- if KORSUVA (CR845/difelikefalin) injection or any of our other current or future product candidates is approved, our ability to establish the necessary commercial infrastructure to launch this product candidate without substantial delays, including hiring sales and marketing personnel and contracting with third parties for warehousing, distribution, cash collection and related commercial activities;

- our ability to identify, enter into and maintain third party manufacturing arrangements capable of manufacturing KORSUVA (CR845/difelikefalin) injection or our other current or future product candidates in commercial quantities;

- our execution of other collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;

- variations in the level of expenses related to our future development programs;

- any product liability or intellectual property infringement lawsuit in which we may become involved;

- regulatory developments affecting KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin), any of our future product candidates, or the product candidates of our competitors; and

- if KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or any of our future product candidates receives regulatory approval, the level of underlying demand for such product candidate and wholesaler buying patterns.

If our quarterly or annual operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly or annual fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

***Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights.***

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

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. Any debt financing that we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

***The use of our net operating loss carryforwards and research tax credits may be limited.***

Our net operating loss, or NOL, carryforwards and R&D tax credits may expire and not be used. As of December 31, 2019, we had federal and state NOL carryforwards of approximately $349.5 million and $189.2 million, respectively, and we also had federal and state R&D tax credit carryforwards of approximately $15.3 million and $1.4 million, respectively. Our NOL carryforwards will begin expiring in 2026 for federal purposes (to the extent such federal

NOLs are generated in taxable years ending on or before December 31, 2017) and 2027 for state purposes if we have not used them prior to that time, and our federal R&D tax credits will begin expiring in 2025 unless previously used. Under the TCJA, the use of NOLs generated in taxable years ending after December 31, 2017 are subject to a limitation of 80% of taxable income, and such NOLs can be carried forward indefinitely (but carryback is generally prohibited). It is uncertain if and to what extent various states will conform to the TCJA. To the extent that we have not exchanged our Connecticut R&D tax credits for a tax refund, those tax credits carryforward indefinitely. Additionally, our ability to use any NOL and R&D tax credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Internal Revenue Code Sections 382 and 383, respectively, if we have a cumulative change in ownership of our stock of more than 50% within a three-year period. The completion of our initial public offering in 2014 and our follow-on public offerings in 2015, 2017, 2018 and 2019, together with private placements and other transactions that have occurred, may have triggered such ownership changes. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo ownership changes in the future. We have never completed an analysis as to whether such a change of ownership has occurred, but in such an event, we will be limited regarding the amount of NOL carryforwards and R&D tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. Any such annual limitation may significantly reduce the utilization of the NOL carryforwards and R&D tax credits before they expire. In addition, certain states have in the past suspended use of NOL carryforwards for certain taxable years, and other states are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, limitations on our ability to use NOL carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

***New or future changes to tax laws could materially adversely affect our company.***

On December 22, 2017, President Trump signed into law the TCJA, which significantly amends the Internal Revenue Code of 1986. The TCJA, among other things, reduces the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limits the tax deduction for interest expense to 30% of taxable income, eliminates certain NOL carrybacks, imposes a one-time tax on offshore earnings at reduced rates regardless of whether they are repatriated, allows immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifies or repeals many business deductions and credits. We continue to examine the impact these changes may have on our business. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA is uncertain and our business and financial condition could be adversely affected. The impact of the TCJA on holders of our common stock is also uncertain and could be adverse.

***Because we do not intend to pay dividends on our common stock, your returns will be limited to any increase in the value of our stock.***

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business and do not anticipate declaring or paying any cash dividends on our common stock for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock, if any. Investors seeking cash dividends should not purchase our common stock.

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

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

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

- our Board of Directors are divided into three classes, with only one class of directors elected each year;
- our stockholders are entitled to remove directors only for cause upon a 66 2/3% vote;
- our stockholders are not permitted to take actions by written consent;
- our stockholders are not permitted to call a special meeting of stockholders; and
- our stockholders must give us advance notice of their intent to nominate directors or submit proposals for consideration at stockholder meetings.

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

**Item 1B.** ***Unresolved Staff Comments*****.**

None.

**Item 2.** ***Properties*****.**

Our principal offices occupy approximately 24,000 square feet of office space in Stamford, Connecticut under a lease that expires in November 2023. We believe that the office space in Stamford is suitable and adequate to meet our current needs and to allow for expansion as we increase our headcount. See Note 17 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K.

**Item 3.** ***Legal Proceedings*****.**

From time to time, we may become subject to arbitration, litigation or claims arising in the ordinary course of business. We are not currently a party to any arbitration or legal proceeding that, if determined adversely to us, would have a material adverse effect on our business, operating results or financial condition. The results of any future claims or proceedings cannot be predicted with certainty, and regardless of the outcome, litigation can have an adverse impact on us because of defense and litigation costs, diversion of management resources, and other factors.

**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 for Common Stock**

Our common stock is traded on The Nasdaq Global Market under the ticker symbol "CARA".

**Stockholders**

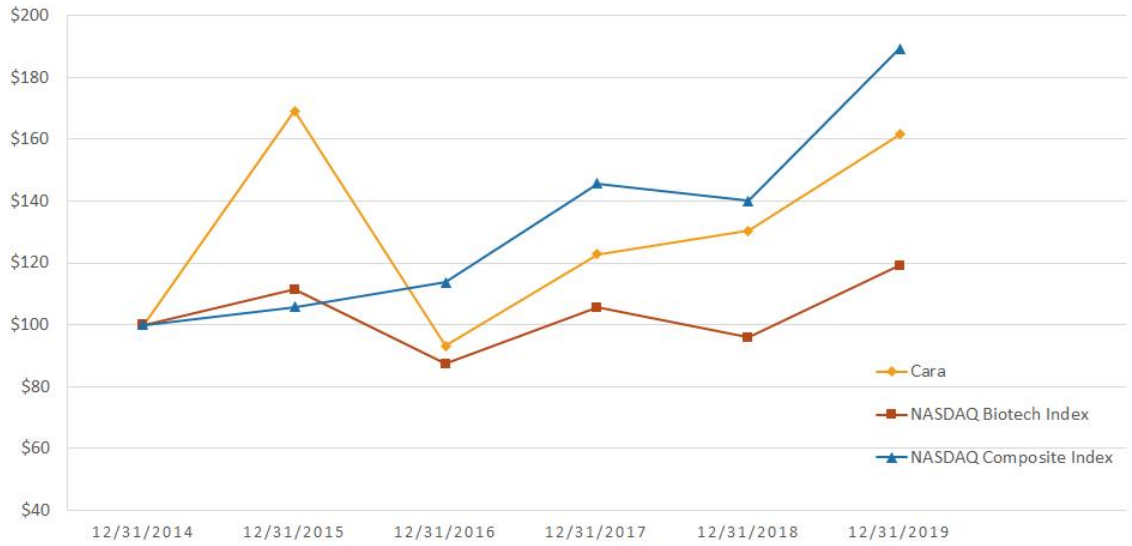
As of February 24, 2020, there were 30 holders of record of our common stock. This number does not reflect the beneficial holders of our common stock who hold shares in street name through brokerage accounts or other nominees.

**Dividend Policy**

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our Board of Directors and will depend on, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our Board of Directors may deem relevant.

**Stock Performance**

The following graph compares cumulative total return of our common stock with the cumulative total return of (i) the Nasdaq Composite Index, and (ii) the Nasdaq Biotechnology Index. The graph assumes (a) $100 was invested on December 31, 2014 in each of our common stock, the stocks comprising the Nasdaq Composite Index and the stocks comprising the Nasdaq Biotechnology Index, and (b) the reinvestment of dividends. The comparisons shown in the graph are based on historical data and the stock price performance shown in the graph is not necessarily indicative of, or intended to forecast, future performance of our stock.



**Cumulative Total Return**

| | 12/31/2014 | 12/31/2015 | 12/31/2016 | 12/31/2017 | 12/31/2018 | 12/31/2019 |
|---|---|---|---|---|---|---|
| Cara Therapeutics, Inc. | 100.00 | 169.11 | 93.18 | 122.77 | 130.39 | 161.58 |
| Nasdaq Biotechnology | 100.00 | 111.42 | 87.26 | 105.64 | 95.79 | 119.17 |
| Nasdaq Composite | 100.00 | 105.73 | 113.66 | 145.76 | 140.10 | 189.45 |

This performance graph shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or incorporated by reference into any filing of ours under the Securities Act, except as shall be expressly set forth by specific reference to such filing.

**Recent Sales of Unregistered Securities**

Not applicable.

**Purchases of Equity Securities by the Issuer and Affiliated Purchasers**

Not applicable.

**Use of Proceeds**

Not applicable.

**Item 6.** ***Selected Financial Data.***

The following selected financial data for the years ended December 31, 2019, 2018 and 2017 and as of December 31, 2019 and 2018 are derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The following selected financial data for the years ended December 31, 2016 and 2015 and as of December 31, 2017, 2016 and 2015 have been derived from our audited financial statements not included in this report. Our historical results for any prior periods are not necessarily indicative of results to be expected for any future period. The information set forth in the following table should be read in conjunction with *Part II Item 7. Management's*

*Discussion and Analysis of Financial Condition and Results of Operations* and our financial statements and related notes thereto included elsewhere in this Annual Report on Form 10-K.

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | 2017 | 2016 | 2015 |
| | (in thousands, except share and per share data) | | | | |
| **Statement of Operations Data:** | | | | | |
| Revenue: | | | | | |
| License and milestone fee revenue | $ 19,746 | $ 13,436 | $ 530 | $ — | $ 1,710 |
| Collaborative revenue | — | — | 313 | — | 2,093 |
| Clinical compound revenue | 140 | 33 | 68 | 86 | — |
| Total revenue [1] | 19,886 | 13,469 | 911 | 86 | 3,803 |
| Operating expenses: | | | | | |
| Research and development | 113,820 | 75,531 | 48,524 | 49,253 | 21,221 |
| General and administrative | 17,745 | 15,320 | 11,872 | 9,233 | 7,770 |
| Total operating expenses | 131,565 | 90,851 | 60,396 | 58,486 | 28,991 |
| Operating loss | (111,679) | (77,382) | (59,485) | (58,400) | (25,188) |
| Other income | 4,490 | 2,980 | 1,156 | 652 | 101 |
| Loss before benefit from income taxes | (107,189) | (74,402) | (58,329) | (57,748) | (25,087) |
| Benefit from income taxes | 816 | 389 | 204 | 468 | 397 |
| Net loss | $ (106,373) | $ (74,013) | $ (58,125) | $ (57,280) | $ (24,690) |
| Net loss per share: | | | | | |
| Basic and Diluted | $ (2.49) | $ (2.06) | $ (1.86) | $ (2.10) | $ (1.00) |
| Weighted average shares: | | | | | |
| Basic and Diluted | 42,669,333 | 35,892,786 | 31,202,842 | 27,279,008 | 24,620,372 |

| | As of December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | 2017 | 2016 | 2015 |
| | (in thousands) | | | | |
| **Balance Sheet Data:** | | | | | |
| Cash and cash equivalents and marketable securities [2] | $218,165 | $182,779 | $ 92,569 | $ 58,276 | $106,740 |
| Total assets [3] | 232,959 | 190,823 | 97,004 | 63,828 | 110,897 |
| Deferred revenue [4] | 22,262 | 42,009 | — | — | — |
| Total liabilities [3] | 46,246 | 57,193 | 10,224 | 13,103 | 5,853 |
| Total stockholders' equity | 186,713 | 133,630 | 86,780 | 50,725 | 105,044 |

(1) The changes in revenue for the years ended December 31, 2015 to December 31, 2016, December 31, 2017 to December 31, 2018, and December 31, 2018 to December 31, 2019 primarily reflect upfront payments in connection with continuing our collaborative work with Maruishi in 2015, milestone payments earned under our collaborations with Maruishi and CKDP in 2015, a sub-license fee payment received from Maruishi in 2017 and an upfront payment from VFMCRP related to the license agreement entered into in May 2018 and earned by us as work was performed in 2018 and 2019 (refer to "Item 7. *Management's Discussion and Analysis of Financial Condition and Results of Operations — Collaboration and License Agreements"*, Note 11 of Notes to Financial Statements, *Collaboration and License Agreements*, and Note 12 of Notes to Financial Statements, *Revenue Recognition* in this Annual Report on Form 10-K).

(2) The increases in cash and cash equivalents and marketable securities from December 31, 2018 to December 31, 2019, December 31, 2017 to December 31, 2018, and from December 31, 2016 to December 31, 2017 reflects the proceeds from our follow-on offering of our common stock in July 2019 and 2018, respectively, the upfront payment from VFMCRP related to the license agreement entered into in May 2018, the proceeds from our follow-on offering of our common stock in April 2017, and our follow-on offering of our common stock in August 2015, respectively, partially offset by cash used in operating activities for each respective period (refer to Note 9 of Notes to Financial Statements, *Stockholders' Equity*, in this Annual Report on Form 10-K).

(3) On January 1, 2019, we adopted ASC 842, *Leases*. As a result, we recorded an operating lease right-of-use asset within total assets and an operating lease liability (current and non-current) within total liabilities as of December 31, 2019 (refer to Note 2 of Notes to Financial Statements, *Summary of Significant Accounting Policies – Accounting Pronouncements Recently Adopted,* and Note 17 of Notes to Financial Statements, *Commitments and Contingencies – Leases*, in this Annual Report on Form 10-K.

(4) The changes in deferred revenue from December 31, 2018 to December 31, 2019 and December 31, 2017 to December 31, 2018 were due to the upfront payment from VFMCRP related to the license agreement entered into in May 2018 and earned by us as work was performed in 2018 and 2019 (refer to Note 12 of Notes to Financial Statements, *Revenue Recognition*, in this Annual Report on Form 10-K).

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

*You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information 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 and related financing, includes forward-looking statements that involve risks and uncertainties. You should read "Cautionary Note Regarding Forward-Looking Statements" and Item 1A. Risk Factors of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.*

**Overview**

**Introduction**

We are a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral KORs. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), a first-in-class KOR agonist that targets KORs located in the peripheral nervous system and on immune cells.

In our KALM-1 Phase 3 trial and two Phase 2 trials, KORSUVA (CR845/difelikefalin) injection (intravenous formulation) has demonstrated statistically significant reductions in itch intensity and concomitant improvement in pruritus-related quality of life measures in hemodialysis patients with moderate-to-severe CKD-aP. We are continuing to investigate KORSUVA (CR845/difelikefalin) injection in our global KALM-2 Phase 3 trial in hemodialysis patients with moderate-to-severe CKD-aP. We have partnered with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, to commercialize KORSUVA (CR845/difelikefalin) injection in dialysis patients with CKD-aP worldwide, excluding the United States, Japan (Maruishi/sub-licensee Kissei), and South Korea (CKDP). We retain all rights in the United States and will promote KORSUVA (CR845/difelikefalin) injection, if approved, with VFMCRP in U.S. FMCNA dialysis clinics under a profit share agreement.

CR845/difelikefalin has also demonstrated statistically significant pain reduction in clinical trials in patients with moderate-to-severe acute pain in the post-operative setting, without inducing many of the undesirable side effects typically associated with currently available opioid pain therapeutics. We retain rights to all KORSUVA/CR845 formulations and indications worldwide, excluding KORSUVA (CR845/difelikefalin) injection in dialysis patients with CKD-aP under our agreement with VFMCRP for certain ex-U.S. territories and our other license agreements for CR845/difelikefalin in Japan (Maruishi/sub-licensee Kissei) and South Korea (CKDP).

The FDA has conditionally accepted KORSUVA as the trade name for CR845/difelikefalin injection and its safety and efficacy have not been fully evaluated by any regulatory authority.

We were incorporated and commenced operations in 2004, and our primary activities to date have been organizing and staffing our company, developing our product candidates, including conducting preclinical studies and clinical trials of CR845/difelikefalin-based product candidates and raising capital. To date, we have financed our operations primarily

through sales of our equity and debt securities and payments from license agreements. We have no products currently available for sale, and substantially all of our revenue to date has been revenue from license agreements, although we have received nominal amounts of revenue under research grants and the sale of clinical compound.

**Collaboration and License Agreements**

*Vifor Fresenius Medical Care Renal Pharma Ltd.*

In May 2018, we entered into the VFMCRP Agreement, with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, under which we granted VFMCRP a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients worldwide (excluding the United States, Japan and South Korea). We retain full development and commercialization rights for KORSUVA injection for the treatment of CKD-aP in the U.S. except in the dialysis clinics of FMCNA, where we and VFMCRP will promote KORSUVA injection under a profit-sharing arrangement.

Upon entry into the VFMCRP Agreement, VFMCRP made a non-refundable, non-creditable $50 million upfront payment to us and Vifor purchased 1,174,827 shares of our common stock for $20 million, at a premium for the price of $17.024 per share. In addition, we are eligible to receive from VFMCRP regulatory and commercial milestone payments in the aggregate of up to $470 million, consisting of up to $30 million in regulatory milestones and up to $440 million in tiered commercial milestones, all of which are sales-related. We are also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined, of KORSUVA (CR845/difelikefalin) injection in the licensed territories. In the United States, we and VFMCRP will promote KORSUVA (CR845/difelikefalin) injection in the dialysis clinics of FMCNA under a profit-sharing arrangement (subject to the terms and conditions of the VFMCRP Agreement) based on net FMCNA clinic sales recorded by us.

*Maruishi Pharmaceutical Co., Ltd.*

In April 2013, we entered into the Maruishi Agreement with Maruishi in Japan, under which we granted Maruishi an exclusive license, to develop, manufacture and commercialize drug products containing CR845/difelikefalin in Japan in the acute pain and uremic pruritus fields. We and Maruishi are each required to use commercially reasonable efforts, at our respective expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States and Japan, respectively. In addition, we have provided Maruishi specific clinical development services for CR845/difelikefalin in Maruishi's field of use between 2013 and 2015.

Under the terms of the Maruishi Agreement, we received a non-refundable and non-creditable upfront license fee of $15.0 million and are eligible to receive up to an aggregate of $6.0 million in clinical development milestones and $4.5 million in regulatory milestones. In August 2014, we received a clinical development milestone payment of $0.5 million upon completion by Maruishi of a Phase 1 clinical trial in Japan related to CR845/difelikefalin in acute post-operative pain. In October 2015, we received a $1.7 million milestone payment (net of contractual foreign currency exchange adjustments of $0.3 million) related to the initiation by Maruishi of a Phase 2 clinical trial of CR845/difelikefalin in Japan for uremic pruritus. In March 2017, we received a payment of $0.8 million in connection with Maruishi entering into a sub-license agreement with Kissei for the development and sales/marketing of CR845/difelikefalin for the treatment of uremic pruritus in dialysis patients in Japan. We are also eligible to receive tiered royalties, with percentages ranging from the low double digits to the low twenties, based on net sales of products containing CR845/difelikefalin in Japan, if any, and share in any sub-license fees. In addition, in connection with the Maruishi Agreement, Maruishi purchased 842,105 shares of our common stock for an aggregate purchase price of $8.0 million.

*Chong Kun Dang Pharmaceutical Corporation*

In April 2012, we entered into the CKDP Agreement with CKDP in South Korea, under which we granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in South

Korea. We and CKDP are each required to use commercially reasonable efforts, at our respective expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States and South Korea, respectively.

Under the terms of the CKDP Agreement, we received a non-refundable and non-creditable upfront license fee of $0.6 million and are eligible to receive up to an aggregate of $2.3 million in clinical development milestones and $1.5 million in regulatory milestones. In addition, CKDP purchased, 69,444 shares of our common stock in consideration for $0.4 million. During the year ended December 31, 2012, we received $0.6 million, net of foreign taxes, from CKDP upon the completion of a Phase 2 trial of CR845/difelikefalin in pain in the United States and a Phase 1a trial of Oral CR845/difelikefalin for uremic pruritus in the United States. During the year ended December 31, 2015, we met the milestone criteria, as set forth in the CKDP Agreement, for completion of a Phase 1b trial of Oral CR845/difelikefalin for uremic pruritus in the United States and for completion of a Phase 2 trial of CR845/difelikefalin in uremic pruritus patients in the United States for which we received milestone payments totaling $0.6 million (net of South Korean withholding tax) from CKDP. We are also eligible to receive tiered royalties with percentages ranging from the high single digits to the high teens, based on net sales of products containing CR845/difelikefalin in South Korea, if any, and share in any sub-license fees.

**Manufacturing and License Agreements**

*Enteris Biopharma, Inc.*

On August 20, 2019, we entered into the Enteris License Agreement. Pursuant to the Enteris License Agreement, Enteris granted to us a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

As consideration for the licensed rights under the Enteris License Agreement, we paid an upfront fee equal to $8.0 million, consisting of $4.0 million in cash and $4.0 million in shares of our common stock pursuant to the Purchase Agreement as described below. As a result, we recognized $8.0 million of R&D expense related to the Enteris License Agreement during the year ended December 31, 2019.

We are also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low-single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, we have the right, but not the obligation, to terminate our obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. Subject to certain conditions, we may elect to pay 50% of the lump sum due under the Royalty Buyout in shares of our common stock pursuant to the Purchase Agreement.

The Enteris License Agreement will expire on a country-by-country, licensed product-by-licensed product basis upon the later of (1) the expiration (or invalidation) of all valid claims in licensed patent rights that cover such product in such country, (2) the end of the calendar quarter in which generic competition (as defined in the Enteris License Agreement) occurs for such product in such country and (3) ten years from the first commercial sale of such product.

Either party may terminate the Enteris License Agreement upon written notice if the other party has failed to remedy a material breach within 60 days (or 30 days in the case of a material breach of a payment obligation). Enteris may terminate the Enteris License Agreement upon 30 days' written notice to us if we or any of our affiliates formally challenge the validity of any licensed patent rights or assists a third party in doing so. We may terminate the Enteris License Agreement for any reason or no reason (a) prior to receipt of first regulatory approval for a licensed product in the United States for any indication upon 30 days' prior written notice to Enteris or (b) on or after receipt of first regulatory approval for a licensed product in the United States for any indication upon 60 days' prior written notice to Enteris.

In connection with the Enteris License Agreement, on August 20, 2019, we entered into the Purchase Agreement, with Enteris and its affiliate, EBP Holdco LLC, collectively referred to as Purchaser, pursuant to which we issued and sold to Purchaser 170,793 shares of our common stock in a private placement. Such shares were issued in satisfaction of the $4.0 million portion of the upfront fee payable in shares of our common stock pursuant to the Enteris License Agreement and for no additional consideration, based on a purchase price of $23.42 per share, which was equal to the 30-day volume weighted average price of our common stock on August 20, 2019. In addition, if we exercise our Royalty Buyout option, we may elect to make 50% of the payment in stock by issuing additional shares of our common stock valued at the 30-day volume weighted average price of our common stock as of such exercise. Pursuant to the Purchase Agreement, we effected the registration and sale of the shares issued and sold to Purchaser thereunder in accordance with the applicable requirements of the Securities Act, which included the filing of a registration statement with the SEC on September 9, 2019. In addition, the Purchase Agreement includes customary representations, warranties and covenants by us.

*Patheon UK Limited*

On July 8, 2019, we entered into an MSA with Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to us for the drug products specified by us from time to time. Pursuant to the MSA, we have agreed to order from Patheon at least a certain percentage of our commercial requirements for a product under a related Product Agreement. Each Product Agreement that we may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement.

The MSA has an initial term ending December 31, 2023, and will automatically renew after the initial term for successive terms of two years each if there is a Product Agreement in effect, unless either party gives notice of its intention to terminate the MSA at least 18 months prior to the end of the then current term.

Either party may terminate the MSA or a Product Agreement upon written notice if the other party (1) has failed to remedy a material breach within a specified time or (2) is declared insolvent or bankrupt, voluntarily files a petition of bankruptcy or assigns such agreement for the benefit of creditors. We may terminate a Product Agreement (a) upon 90 days' prior written notice if any governmental agency takes any action that prevents us from selling the relevant product in the relevant territory, (b) upon six months' prior written notice if we do not intend to order manufacturing services due to a product's discontinuance in the market, or (c) upon 90 days' prior written notice if we determine that the manufacture or supply of a product likely infringes third-party rights. Patheon may terminate the MSA or a Product Agreement (i) upon six months' prior written notice if we assign such agreement to an assignee that is unacceptable to Patheon for certain reasons, or (ii) upon 30 days' prior written notice if, after the first year of commercial sales, we forecast zero volume for 12 months.

The MSA contains, among other provisions, customary representations and warranties by the parties, a grant to Patheon of certain limited license rights to our intellectual property in connection with Patheon's performance of the services under the MSA, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions.

On July 8, 2019, and July 9, 2019, we entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of CR845/difelikefalin injection, our lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of CR845/difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from active pharmaceutical ingredient supplied by us. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product.

**Components of Operating Results**

***Revenue***

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the foreseeable future. Substantially all of our revenue recognized to date has consisted of upfront payments under license agreements with VFMCRP, Maruishi and CKDP, and milestone and sub-license payments under license agreements with CKDP and Maruishi for CR845/difelikefalin, some or all of which was deferred upon receipt, as well as license agreements for CR665, our first-generation drug program for which development efforts have ceased and clinical compound sales from certain license agreements. To date, we have earned a total of $5.4 million in clinical development or regulatory milestone payments, sub-license fees under our Maruishi and CKDP collaborations, net of contractual foreign currency adjustments and South Korean withholding taxes, and clinical compound sales from certain license agreements. We have not yet received any milestone payments under the VFMCRP Agreement or royalties under any of our collaborations.

***Research and Development (R&D)***

Our R&D expenses relate primarily to the development of CR845/difelikefalin. R&D expenses consist of expenses incurred in performing R&D activities, including compensation and benefits for full-time R&D employees, clinical trial and related clinical manufacturing expenses, third-party formulation expenses, fees paid to contract research organizations, or CROs, and other consultants, stock-based compensation for R&D employees and consultants and other outside expenses. Our R&D expenses also included expenses related to preclinical activities for our earlier stage programs in prior periods and may include such expenses in the future.

R&D costs are expensed as incurred. Non-refundable advance payments for goods or services to be received in the future for use in R&D activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed. Most of our R&D costs have been external costs, which we track on a program-by program basis. Our internal R&D costs are primarily compensation expenses for our full-time R&D employees. We do not track internal R&D costs on a program-by-program basis.

R&D activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. Based on our current development plans, we presently expect that our R&D expenses for 2020 will increase over those for 2019. However, it is difficult to determine with certainty the duration and completion costs of our current or future nonclinical programs and clinical trials of our product candidates, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors including, but not limited to:

- per patient trial costs;
- the number of patients that participate in the trials;
- the number of sites included in the trials;
- the countries in which the trial is conducted;
- the length of time required to enroll eligible patients;
- the number of doses that patients receive;

- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the duration of patient follow-up; and
- the efficacy and safety profile of the product candidate.

In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential.

***General and Administrative***

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, legal, business development, information technology and human resources functions. Other costs include facility costs not otherwise included in R&D expenses, legal fees, insurance costs, investor relations costs, patent costs and fees for accounting and consulting services.

We anticipate that our general and administrative expenses for 2020 will increase as compared to 2019 to support our continued R&D activities and potential commercialization of our product candidates. These expenses will likely include costs related to the hiring of additional personnel, fees to outside consultants, lawyers, accountants and investor relations firms. In addition, if I.V. CR845/difelikefalin, Oral CR845/difelikefalin or any future product candidate obtains regulatory approval for marketing, we expect to incur expenses associated with building a sales and marketing team.

***Other Income***

Other income consists of interest and dividend income earned on our cash, cash equivalents, marketable securities and restricted cash, realized gains and losses on the sale of marketable securities and property and equipment as well as accretion of discounts/amortization of premiums on purchases of marketable securities.

***Benefit from Income Taxes***

The benefit from income taxes relates to state R&D tax credits exchanged for cash pursuant to the Connecticut R&D Tax Credit Exchange Program, which permits qualified small businesses engaged in R&D activities within Connecticut to exchange their unused R&D tax credits for a cash amount equal to 65% of the value of the exchanged credits.

**Results of Operations**

***Comparison of the years ended December 31, 2019, 2018 and 2017***

**Revenue**

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | | 2017 | |
| | Dollar amounts in thousands | | | | |
| | | % change | | % change | |
| License and milestone fees revenue | $ 19,746 | 47 % | $ 13,436 | 2,436 % | $ 530 |
| Collaborative revenue | — | — % | — | (100)% | 313 |
| Clinical compound revenue | 140 | 320 % | 33 | (51)% | 68 |
| Total revenue | $ 19,886 | 48 % | $ 13,469 | 1,379 % | $ 911 |

*License and milestone fee revenue*

License and milestone fees revenue of $19.7 million and $13.4 million for the years ended December 31, 2019 and 2018, respectively, were related to license fees earned by us during the respective periods in connection with the VFMCRP Agreement. License and milestone fees revenue for the year ended December 31, 2017 included $530 thousand of the $843 thousand sub-license fee earned by us in connection with Maruishi's sub-license agreement with Kissei that was allocated to the license fee deliverable under the Maruishi Agreement (see Note 11 of Notes to Financial Statements, *Collaboration and Licensing Agreements*, in this Annual Report on Form 10-K).

*Collaborative revenue*

There was no collaborative revenue for the years ended December 31, 2019 and 2018. Collaborative revenue for the year ended December 31, 2017 included $313 thousand of the $843 thousand sub-license fee earned by us in connection with Maruishi's sub-license agreement with Kissei that was allocated to the R&D services deliverable under the Maruishi Agreement (see Note 11 of Notes to Financial Statements, *Collaboration and Licensing Agreements*, in this Annual Report on Form 10-K).

*Clinical compound revenue*

Clinical compound revenue of $140 thousand, $33 thousand and $68 thousand for the years ended December 31, 2019, 2018 and 2017, respectively, related to the sale of clinical compound to Maruishi.

**Research and Development Expense**

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | | 2018 | | 2017 |
| | Dollar amounts in thousands | | | | |
| | | % change | | % change | |
| Direct clinical trial costs | $ 80,098 | 41 % | $ 56,625 | 66 % | $ 34,075 |
| Consultant services in support of clinical trials | 4,470 | 31 % | 3,406 | 74 % | 1,959 |
| Stock-based compensation | 5,809 | 32 % | 4,395 | 81 % | 2,433 |
| Depreciation and amortization | 110 | (62)% | 288 | (31)% | 418 |
| Other R&D operating expenses | 23,333 | 116 % | 10,817 | 12 % | 9,639 |
| Total R&D expense | $113,820 | 51 % | $ 75,531 | 56 % | $ 48,524 |

For the year ended December 31, 2019 compared to the year ended December 31, 2018, the net increase in direct clinical trial costs and related consultant costs primarily resulted from increases totaling $32.7 million, mainly from activities related to the two Phase 3 efficacy trials and up to 12 week Phase 3 safety trial of KORSUVA (CR845/difelikefalin) injection in CKD patients undergoing hemodialysis, the Phase 2 efficacy trial of Oral CR845 in CKD-aP patients, the Phase 2 efficacy trial for CLD-aP and the Phase 2 efficacy trial for pruritus associated with AD. There was also an increase of $1.6 million in drug manufacturing costs. Those costs were partially offset by a decrease of $9.4 million, mainly from the Phase 2/3 I.V. CR845/difelikefalin adaptive clinical trial in post-operative pain and costs associated with certain Phase 1 studies. The increase in stock-based compensation expense was primarily the result of additional stock option grants to R&D employees. The increase in other R&D operating expenses primarily resulted from the upfront payment of $8.0 million upon entering into the Enteris License Agreement and an increase in payroll and related costs associated with R&D personnel.

For the year ended December 31, 2018 compared to the year ended December 31, 2017, the net increase in direct clinical trial costs and related consultant costs primarily resulted from increases totaling $37.7 million, mainly from activities related to the two Phase 3 studies of KORSUVA (CR845/difelikefalin) injection in CKD patients undergoing hemodialysis, the Phase 3 long-term safety study of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP, the Phase 2 trial of Oral CR845 in CKD-aP patients and the Phase 1 safety and PK trial of Oral CR845/difelikefalin in patients with liver disease. There was also an increase of $4.0 million in drug manufacturing costs. Those costs were partially offset by a decrease of $17.2 million, mainly from the Phase 2b clinical trial of Oral

CR845/difelikefalin in patients with osteoarthritis, the Phase 2/3 I.V. CR845/difelikefalin adaptive clinical trial in postoperative pain, the Phase 2 clinical trial of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with moderate-to-severe uremic pruritus and the Phase 1 safety and PK trial of multiple doses of Oral CR845/difelikefalin in hemodialysis patients, all of which are complete and no longer ongoing. The increase in stock-based compensation expense relates primarily to an increase in the number of options outstanding, which includes options granted to our new CMO in October 2018, as well as the vesting of restricted stock units granted to our other R&D executive officers. The increase in other R&D operating expenses was primarily the result of an increase in payroll and related costs associated with R&D personnel, partially offset by lower costs associated with conferences.

The following table summarizes our R&D expenses by product candidate for the years ended December 31, 2019, 2018 and 2017:

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | | 2018 | | 2017 |
| | Dollar amounts in thousands | | | | |
| | | % change | | % change | |
| External research and development expenses: | | | | | |
| I.V. CR845 - Pruritus | $ 59,687 | 67 % | $ 35,781 | 373 % | $ 7,566 |
| I.V. CR845 - Pain | 373 | (94)% | 6,386 | (52)% | 13,226 |
| Oral CR845 - Pruritus | 24,475 | 56 % | 15,670 | 138 % | 6,594 |
| Oral CR845 - Pain | 33 | (98)% | 2,194 | (75)% | 8,648 |
| Internal research and development expenses | 29,252 | 89 % | 15,500 | 24 % | 12,490 |
| Total research and development expenses | $ 113,820 | 51 % | $ 75,531 | 56 % | $ 48,524 |

**General and Administrative Expense**

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | | 2018 | | 2017 |
| | Dollar amounts in thousands | | | | |
| | | % change | | % change | |
| Professional fees and public/investor relations | $ 3,883 | 34 % | $ 2,906 | 29 % | $ 2,252 |
| Stock-based compensation | 6,759 | 19 % | 5,700 | 46 % | 3,897 |
| Depreciation and amortization | 88 | 7 % | 82 | 6 % | 77 |
| Other G&A operating expenses | 7,015 | 6 % | 6,632 | 17 % | 5,646 |
| Total G&A expense | $ 17,745 | 16 % | $ 15,320 | 29 % | $ 11,872 |

For the year ended December 31, 2019 compared to the year ended December 31, 2018, the increase in professional fees and public/investor relations expenses was primarily the result of increased consultants' costs and legal and accounting fees. The increase in stock-based compensation expense was primarily the result of additional stock option grants to G&A employees, additional stock-based compensation expense relating to restricted stock units granted to the members of our Board of Directors in June 2019, and stock-based compensation expense resulting from issuing shares of our common stock for consulting services performed during the year ended December 31, 2019. The increase in other G&A operating expenses was primarily the result of an increase in insurance costs and franchise taxes, partially offset by a decrease in rent, utilities and related costs.

For the year ended December 31, 2018 compared to the year ended December 31, 2017, the increase in professional fees and public/investor relations expenses was primarily the result of increased consultants' costs and legal fees. The increase in stock-based compensation expense resulted from additional stock option grants to employees as well as the vesting of restricted stock units granted to G&A executive officers. The increase in other G&A operating expenses was primarily the result of an increase in payroll and related costs associated with G&A personnel, partially offset by a decrease in rent, utilities and related costs.

**Other Income**

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | | | 2017 |
| | Dollar amounts in thousands | | | | |
| | | % change | | % change | |
| Other income | $ 4,490 | 51 % | $ 2,980 | 158 % | $ 1,156 |

For the year ended December 31, 2019 compared to the year ended December 31, 2018, the increase in other income was primarily due to an increase in interest and accretion income resulting from a higher average balance of our portfolio of investments in the 2019 period.

For the year ended December 31, 2018 compared to the year ended December 31, 2017, the increase in other income was primarily due to an increase in dividend and interest income resulting from a higher average balance of our portfolio of investments in the 2018 period.

**Benefit from Income Taxes**

For the years ended December 31, 2019, 2018 and 2017, pre-tax losses were $107.2 million, $74.4 million and $58.3 million, respectively, and we recognized a benefit from income taxes of $816 thousand, $389 thousand and $204 thousand, respectively.

The benefit from income taxes relates to state R&D tax credits exchanged for cash pursuant to the Connecticut R&D Tax Credit Exchange Program, as discussed above. We recognized a full valuation allowance against deferred tax assets at December 31, 2019, 2018 and 2017.

**Liquidity and Capital Resources**

***Sources of Liquidity***

Since our inception and through December 31, 2019, we have raised an aggregate of $623.2 million to fund our operations, including (1) net proceeds of $446.3 million from the sale of shares of our common stock in five public offerings, including our initial public offering; (2) proceeds of $73.3 million from the sale of shares of our convertible preferred stock and from debt financings prior to our initial public offering; (3) payments of $89.0 million under our license agreements, primarily with VFMCRP, Maruishi, CKDP and an earlier product candidate for which development efforts ceased in 2007; and (4) net proceeds of $14.6 million from the purchase of our common stock in relation to the license agreement with VFMCRP (see Note 11 of Notes to Financial Statements, *Collaboration and Licensing Agreements*, in this Annual Report on Form 10-K).

In order to fund our future operations, including our planned clinical trials, we filed the Shelf Registration Statement (File No. 333-230333), which provides for aggregate offerings of up to $300.0 million of common stock, preferred stock, debt securities, warrants or any combination thereof and was declared effective on April 4, 2019. The securities registered under the Shelf Registration Statement include unsold securities that had been registered under our previous Registration Statement on Form S-3 (File No. 333-216657) that was declared effective on March 24, 2017. We believe that our Shelf Registration Statement provides us with the flexibility to raise additional capital to finance our operations as needed.

On July 24, 2019, we entered into an underwriting agreement with J.P. Morgan Securities LLC and Jefferies LLC, as representatives of the several underwriters named therein, relating to the issuance and sale by us of up to 6,325,000 shares of our common stock, including 825,000 additional shares of common stock that the underwriters had the option to purchase, at a public offering price of $23.00 per share. We closed this offering on July 29, 2019, including the full exercise of the underwriters' option to purchase additional shares of common stock. We received net proceeds of $136.5 million, after deducting $9.0 million of underwriting discounts and commissions and offering expenses. This offering

was made by pursuant to the Shelf Registration Statement, and a related prospectus supplement dated July 24, 2019, which was filed with the SEC on July 25, 2019.

We may offer additional securities under our Shelf Registration Statement from time to time in response to market conditions or other circumstances if we believe such a plan of financing is in the best interests of our stockholders.

As of December 31, 2019, we had $218.2 million in unrestricted cash and cash equivalents and available-for-sale marketable securities. We believe our current unrestricted cash and cash equivalents and available-for-sale marketable securities will be sufficient to fund our currently anticipated operating expenses and capital expenditures into the second half of 2021, without giving effect to any potential milestone payments we may receive under our licensing and collaboration agreements with VFMCRP, Maruishi and CKDP. Our anticipated operating expenses include contractually committed costs as well as non-contractually committed clinical trial costs for trials that may be delayed or not initiated and other non-committed controllable costs.

Under the VFMCRP Agreement, we are eligible to receive regulatory and commercial milestone payments in the aggregate of up to $470 million, consisting of up to $30 million in regulatory milestones and up to $440 million in tiered commercial milestones, all of which are sales-related. We are also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined in the VFMCRP Agreement, of CR845/difelikefalin injection in the Licensed Territories. As of December 31, 2019, we have not received any milestone payments under the VFMCRP Agreement.

Under the Maruishi Agreement, we are also potentially eligible to earn up to an aggregate of $6.0 million in clinical development milestones and $4.5 million in regulatory milestones, before any foreign exchange adjustment, as well as tiered royalties, with percentages ranging from the low double digits to the low twenties, based on net sales of products containing CR845/difelikefalin in Japan, if any, and share in any sub-license fees. As of December 31, 2019, we have received milestone payments of $2.5 million before contractual foreign currency exchange adjustments under the Maruishi Agreement.

Under the CKDP Agreement, we are potentially eligible to earn up to an aggregate of $2.3 million in clinical development milestones and $1.5 million in regulatory milestones, before South Korean withholding tax, as well as tiered royalties with percentages ranging from the high single digits to the high teens, based on net sales of products containing CR845/difelikefalin in South Korea, if any, and share in any sub-license fees. As of December 31, 2019, we have received milestone payments of $1.5 million before South Korean withholding tax under the CKDP Agreement.

Our ability to earn these payments and their timing is dependent upon the outcome of I.V. and Oral CR845/difelikefalin development activities and, potentially, commercialization. However, our receipt of any further such amounts is uncertain at this time and we may never receive any more of these amounts.

***Funding Requirements***

Our primary uses of capital have been, and we expect will continue to be, compensation and related expenses, third-party clinical R&D services and clinical costs. In the past, we have also previously used capital for laboratory and related supplies.

Since inception, we have incurred significant operating and net losses. Our net losses were $106.4 million, $74.0 million and $58.1 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $400.7 million. We expect to continue to incur significant expenses and operating and net losses in the near future. Our net losses may fluctuate significantly from quarter to quarter and year to year, depending on the timing of our clinical trials, the receipt of additional milestone payments, if any, under our licensing and collaborations with VFMCRP, Maruishi and CKDP, the receipt of payments under any future collaborations and/or licensing agreements we may enter into, and our expenditures on other R&D activities.

We anticipate that our expenses will increase as we:

- continue the development of KORSUVA (CR845/difelikefalin) injection for CKD-aP in dialysis patients;
- continue the development of Oral KORSUVA (CR845/difelikefalin) for CKD-aP and other diseases associated with pruritus, such as CLD-aP and AD;
- explore the potential to further develop I.V. CR845/difelikefalin in the post-operative setting;
- conduct R&D of any potential future product candidates;
- seek regulatory approvals for I.V. CR845/difelikefalin and any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval;
- maintain, expand and protect our global intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts.

The successful development of any of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the development of I.V. CR845/difelikefalin, Oral CR845/difelikefalin or our other current and future programs. We are also unable to predict when, if ever, we will generate any further material net cash inflows from CR845/difelikefalin. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- successful enrollment in, and completion of clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- achieving meaningful penetration in the markets which we seek to serve; and
- obtaining adequate coverage or reimbursement by third parties, such as commercial payers and government healthcare programs, including Medicare and Medicaid.

A change in the outcome of any of these variables with respect to the development of I.V. CR845/difelikefalin, Oral CR845/difelikefalin or any of our future product candidates would significantly change the costs and timing associated with the development of that product candidate.

Because our product candidates are still in clinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development and commercialization of all our product candidates or whether, or when, we may achieve profitability. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or debt financings and collaboration arrangements, including our existing licensing and collaboration agreements with VFMCRP, Maruishi and CKDP.

We will require additional capital beyond our current balances of cash and cash equivalents and available-for-sale marketable securities and anticipated amounts as described above, and this additional capital may not be available when needed, on reasonable terms, or at all. In particular, because we do not have sufficient financial resources to meet all of our development objectives, especially the completion of our planned development of I.V. and Oral CR845/difelikefalin for the treatment of pruritus, we will need to raise additional capital. If we are not able to do so, we could be required to postpone, scale back or eliminate some, or all, of these objectives. To the extent that we raise additional capital through the future sale of equity or convertible debt, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through the issuance of debt securities, these securities could contain covenants that would restrict our operations. If we raise additional funds through collaboration arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our drug development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

***Outlook***

Based on timing expectations and projected costs for our current clinical development plans, which include completing our Phase 3 trials of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients suffering from moderate-to-severe CKD-aP to enable the submission of a new drug application, conducting supportive Phase 1 trials and Phase 2 trials of Oral KORSUVA (CR845/difelikefalin) in patients with pruritus associated with CKD, CLD and AD, we expect that our existing cash and cash equivalents and available-for-sale marketable securities as of December 31, 2019 will be sufficient for us to fund our currently anticipated operating expenses and capital expenditures into the second half of 2021, without giving effect to any potential milestone payments we may receive under our collaboration agreements with VFMCRP, Maruishi and CKDP. Our anticipated operating expenses include contractually committed costs as well as non-contractually committed clinical trial costs for trials that may be delayed or not initiated and other non-committed controllable costs. Because the process of testing product candidates in clinical trials is costly and the timing of progress in these trials is uncertain, it is possible that the assumptions upon which we have based this estimate may prove to be wrong, and we could use our capital resources sooner than we presently expect.

***The Tax Cuts and Jobs Act of 2017***

On December 22, 2017, the TCJA was enacted in the United States. Under generally accepted accounting principles in the United States, or GAAP, the effect of a change in tax rates and tax law is recorded discretely as a component of the income tax provision related to continuing operations in the period of enactment. Under the TCJA, among other provisions, the maximum Federal corporate tax rate is reduced from 35% to 21% for tax years beginning after December 31, 2017.

Accounting Standards Codification, or ASC, section 740, *Income Taxes*, requires deferred tax assets and liabilities to be measured at the enacted tax rate expected to apply when temporary differences are to be realized or settled. Therefore, at the date of enactment, we reduced deferred tax assets by $25.9 million based on the revised tax rate, which required a re-assessment of the related valuation allowance. Based on expected net losses into the foreseeable future, we will currently continue to record a 100% valuation allowance against our deferred tax assets. The corresponding reduction in the valuation allowance as a result of the re-measurement of deferred tax assets and liabilities was also recorded to continuing operations in the tax provision. As of December 31, 2019 and 2018, we did not have any foreign subsidiaries and the international aspects of the TCJA are not applicable for the respective periods.

In addition, NOLs arising after December 31, 2017, can be carried forward indefinitely but carryback is generally prohibited. The use of such NOL carryforwards is limited to 80% of taxable income. NOLs generated before January 1, 2018 will not be subject to the taxable income limitation and will continue to have a two-year carryback and 20-year carryforward period.

On December 22, 2017, Staff Accounting Bulletin 118, or SAB 118, was issued by the SEC due to the complexities involved in accounting for the TCJA. SAB 118 requires us to include in our financial statements a reasonable estimate of the impact of the TCJA on earnings to the extent such estimate has been determined. Accordingly, our U.S. provision for income tax for 2017 was based on the reasonable estimate guidance provided by SAB 118. We finalized the accounting for the TCJA as of December 31, 2018, which resulted in insignificant adjustments.

***Cash Flows***

The following is a summary of the net cash flows provided by (used in) our operating, investing and financing activities for the years ended December 31, 2019, 2018 and 2017:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| | Dollar amounts in thousands | | |
| Net cash used in operating activities | $(109,225) | $ (22,301) | $(54,827) |
| Net cash used in investing activities | (30,516) | (82,819) | (36,500) |
| Net cash provided by financing activities | 142,604 | 110,813 | 87,923 |
| Net increase (decrease) in cash, cash equivalents and restricted cash | $ 2,863 | $ 5,693 | $ (3,404) |

***Net cash used in operating activities***

Net cash used in operating activities for the year ended December 31, 2019 consisted primarily of a net loss of $106.4 million and a $3.8 million cash outflow from net non-cash charges, partially offset by a $0.9 million cash inflow from net changes in operating assets and liabilities. Net non-cash charges primarily consisted of a decrease of $19.7 million in deferred revenue associated with our VFMCRP Agreement and $1.4 million related to accretion of available-for-sale securities, partially offset by stock-based compensation expense of $12.6 million and a noncash expense of $4.0 million related to the Enteris License Agreement. The change in operating assets and liabilities primarily consisted of a cash inflow of $6.0 million from an increase in accounts payable and accrued expenses, partially offset by a cash outflow of $4.1 million from an increase in prepaid expense, primarily related to an increase in prepaid clinical costs and a cash outflow of $0.9 million from operating lease liability relating to lease payments made for the Stamford Lease as a result of our adoption of ASC 842: Leases.

Net cash used in operating activities for the year ended December 31, 2018 consisted primarily of a net loss of $74.0 million, partially offset by a $50.5 million cash inflow from net non-cash charges and a $1.2 million inflow from net changes in operating assets and liabilities. Net non-cash charges primarily consisted of an increase in deferred revenue of $42.0 million related to the VFMCRP Agreement and stock-based compensation expense of $10.1 million, partially offset by $1.8 million related to amortization/accretion of available-for-sale securities. The net change in operating assets and liabilities primarily consisted of a cash inflow of $5.1 million from an increase in accounts payable and accrued expenses, partially offset by cash outflows of $3.2 million from an increase in prepaid expense, primarily related to an increase in prepaid clinical costs, and cash outflows of $0.8 million related to an increase in other receivables.

Net cash used in operating activities for the year ended December 31, 2017 consisted primarily of a net loss of $58.1 million, a $3.0 million outflow from net changes in operating assets and liabilities and a $6.3 million cash inflow from net non-cash charges. The net change in operating assets and liabilities primarily consisted of cash outflows of $3.0 million from a decrease in accounts payable and accrued expenses. Net non-cash charges primarily consisted of stock-

based compensation expense of $6.3 million and depreciation and amortization expense of $0.5 million, partially offset by accretion/amortization on available-for-sale securities of $0.6 million.

***Net cash used in investing activities***

Net cash used in investing activities was $30.5 million for the year ended December 31, 2019, which primarily included cash outflows of $286.1 million for the purchases of available-for-sale marketable securities, partially offset by $255.6 million from maturities and redemptions of available-for-sale marketable securities.

Net cash used in investing activities was $82.8 million for the year ended December 31, 2018, which primarily included cash outflows of $337.9 million for the purchase of available-for-sale marketable securities, partially offset by cash inflows of $175.3 million from maturities of available-for-sale marketable securities and $79.8 million from the sale of available-for-sale marketable securities.

Net cash used in investing activities for the year ended December 31, 2017, primarily included cash outflows of $127.4 million from the purchase of available-for-sale securities. Those cash outflows were partially offset by cash inflows of $82.2 million from maturities of available-for-sale securities and $8.8 million from the sale of available-for-sale securities.

***Net cash provided by financing activities***

Net cash provided by financing activities for the year ended December 31, 2019 consisted of gross proceeds of $145.5 million from our issuance and sale of our common stock in July 2019, partially offset by $9.0 million of underwriting discounts and commissions and offering expenses paid by us during the year ended December 31, 2019, and proceeds of $6.1 million received from the exercise of stock options.

Net cash provided by financing activities for the year ended December 31, 2018 consisted of gross proceeds of $98.3 million from our issuance and sale of our common stock in July 2018, partially offset by $6.3 million of underwriting discounts and commissions and offering expenses paid by us during the year ended December 31, 2018, proceeds of $14.6 million from the sale of our common stock relating to the VFMCRP Agreement and $4.2 million received from the exercise of stock options.

Net cash provided by financing activities for the year ended December 31, 2017 consisted primarily of gross proceeds of $92.1 million from our follow-on offering of common stock, partially offset by $5.9 million of underwriting discounts and commissions and offering expenses paid by us during the year ended December 31, 2017, and proceeds of $1.7 million received from stock option exercises.

**Contractual Obligations**

The following table summarizes our significant contractual obligations as of December 31, 2019 (in thousands):

| | Payment Due for the Year Ending December 31, | | | | | |
|---|---|---|---|---|---|---|
| | 2020 | 2021 | 2022 | 2023 | 2024 | Total |
| Stamford operating lease | $ 1,239 | $ 1,264 | $ 1,288 | $ 1,164 | $ — | $ 4,955 |

Contractual obligations and commitments at December 31, 2019 also included the Enteris License Agreement, which we entered into in August 2019, and the MSA we entered into with Patheon in July 2019. However, we have no material non-cancelable purchase commitments with these contract manufacturers or service providers, as we have generally contracted on a cancelable purchase order basis. Therefore, these were not included in the table above. Furthermore, milestone payments potentially owed by us in connection with the Enteris License Agreement were not included in the table above as these milestone events may or may not be achieved.

See Note 17 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K for details about our contractual obligations and commitments.

**Off-Balance Sheet Arrangements**

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under SEC rules.

**Critical Accounting Policies and Significant Judgments and Estimates**

Our management's discussion and analysis of financial condition and results of operations is based upon our financial statements, which have been prepared in accordance with GAAP. The preparation of these financial statements requires us to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities as of the date of the balance sheets and the reported amounts of revenues and expenses during the reporting periods. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances at the time such estimates are made. Actual results and outcomes may differ materially from our estimates, judgments and assumptions. We periodically review our estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates are reflected in the financial statements prospectively from the date of the change in estimate.

We define our critical accounting policies as those accounting principles generally accepted in the United States that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as well as the specific manner in which we apply those principles. We believe the critical accounting policies used in the preparation of our financial statements which require significant estimates and judgments are as follows:

***Revenue Recognition***

On January 1, 2018, we adopted Accounting Standards Update, or ASU, 2014-09, *Revenue from Contracts with Customers (Topic 606)*, or ASC 606, as amended by ASU 2016-08, 2016-10, 2016-12 and 2016-20 using the full retrospective method. Under ASC 606, we recognize revenue in an amount that reflects the consideration to which we expect to be entitled in exchange for the transfer of promised goods or services to customers. To determine revenue recognition for contracts with customers that are within the scope of ASC 606, we perform the following steps: (1) identify the contract with the customer, (2) identify the performance obligations in the contract, (3) determine the transaction price, (4) allocate the transaction price to the performance obligations in the contract, and (5) recognize revenue when (or as) the entity satisfies a performance obligation. We have concluded that upon adoption of ASC 606, as amended, there was no impact on our results of operations, financial position or cash flows for any period presented from our only two revenue-related contracts, which were in effect at that time: the CKDP Agreement or the Maruishi Agreement.

We have entered into agreements to license our intellectual property, or IP, related to CR845/difelikefalin to develop, manufacture and/or commercialize drug products. These agreements typically contain multiple performance obligations, including licenses of IP and R&D services. Payments to us under these agreements may include nonrefundable license fees, payments for research activities, payments based upon the achievement of certain milestones and royalties on any resulting net product sales.

We identify agreements as contracts that create enforceable rights and obligations when the agreement is approved by the parties, identifies the rights of the parties and the payment terms, has commercial substance and it is probable that we will collect the consideration to which we will be entitled in exchange for the goods and services that will be transferred to the customer. The counterparty is considered to be a customer when it has contracted with us to obtain goods and services that are the output of our ordinary activities (i.e., development of pharmaceutical products) in exchange for consideration.

A performance obligation is a promise to transfer distinct goods or services to a customer. Performance obligations that are both capable of being distinct and distinct within the context of the contract are considered to be separate performance obligations. Performance obligations are capable of being distinct if the counterparty is able to benefit from the good or service on its own or together with other resources that are readily available to it. Performance obligations

are distinct within the context of the contract when each performance obligation is separately identifiable from each other; i.e., we are not using the goods or services as inputs to produce or deliver the combined output or outputs specified by the customer; one or more of the goods or services does not significantly modify or customize one of the other goods or services in the contract; and goods or services are not highly interdependent or not highly interrelated. Performance obligations that are not distinct are accounted for as a single performance obligation over the period that goods or services are transferred to the customer. The determination of whether performance obligations in a contract are distinct may require significant judgment.

The transaction price is the amount of consideration that we expect to be entitled to in exchange for transferring promised goods or services to the customer based on the contract terms at inception of a contract. There is a constraint on inclusion of variable consideration related to licenses of IP, such as milestone payments or sales-based royalty payments, in the transaction price if there is uncertainty at inception of the contract as to whether such consideration will be recognized in the future because it is probable that there will be a significant reversal of revenue in the future when the uncertainty is resolved. The determination of whether or not it is probable that a significant reversal of revenue will occur in the future depends on the likelihood and magnitude of the reversal. Factors that could increase the likelihood or magnitude of a reversal of revenue include (a) the susceptibility of the amount of consideration to factors outside the entity's influence, such as the outcome of clinical trials, the timing of initiation of clinical trials by the counterparty and the approval of drug product candidates by regulatory agencies, (b) situations in which the uncertainty is not expected to be resolved for a long period of time, and (c) level of our experience in the field. When it becomes probable that events will occur, for which variable consideration was constrained at inception of the contract, we allocate the related consideration to the separate performance obligations in the same manner as described below.

At inception of a contract, we allocate the transaction price to the distinct performance obligations based upon their relative standalone selling prices. Standalone selling price is the price at which an entity would sell a promised good or service separately to a customer. The best evidence of standalone selling price is an observable price of a good or service when sold separately by an entity in similar circumstances to similar customers. Since we typically do not have such evidence, we estimate standalone selling price so that the amount that is allocated to each performance obligation equals the amount that we expect to receive for transferring goods or services. The methods that we use to make such estimates include (1) the adjusted market assessment approach, under which we forecast and analyze CR845/difelikefalin in the appropriate market, the phase of clinical development as well as considering recent similar license arrangements within the same phase of clinical development, therapeutic area, type of agreement, etc. and (2) the expected cost of satisfying the performance obligations plus a margin, or the expected cost plus a margin approach.

We recognize revenue when, or as, we satisfy a performance obligation by transferring a promised good or service to a customer and the customer obtains control of the good or service. Revenue related to the grant of a license that is a distinct performance obligation and that is deemed to be functional IP is recognized at the point in time that we have the right to payment for the license, the customer has legal title to the license and can direct the use of the license (for example, to grant sublicenses), the customer has the significant risks and rewards of ownership of the license and the customer has accepted the asset (license) by signing the license agreement.

Recognition of revenue related to R&D services that are a distinct performance obligation or that are combined with granting of a license as a single performance obligation is deferred at inception of a contract and is recognized as those services are performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation.

Milestone payments are considered to be variable consideration and are not included in the transaction price at inception of the contract if it is uncertain that the milestone will be achieved. Rather, when it becomes probable that the milestone will be achieved and, therefore, there will not be a significant reversal of revenue in future periods, the respective amount to be earned is included in the transaction price, allocated to the distinct performance obligations based on their relative standalone selling price and recognized as revenue, as described above. Sales milestones and sales-based royalty payments related to a license of IP are recognized as revenue when the respective sales occur.

***Stock-Based Compensation***

We grant stock options to employees, non-employee directors and non-employee consultants as compensation for services performed. Employee and non-employee members of the Board of Directors' awards of stock-based compensation are accounted for in accordance with ASC 718, *Compensation - Stock Compensation*, or ASC 718. ASC 718 requires all share-based payments to employees and non-employee directors, including grants of stock options, to be recognized in the Statements of Comprehensive Loss based on their grant date fair values. The grant date fair value of stock options is estimated using the Black-Scholes option valuation model. For all share-based payments granted to employees and non-employees, compensation cost relating to awards with service-based graded vesting schedules is recognized using the straight-line method over the requisite service period.

Using this model, fair value is calculated based on (i) the fair value or market price of our common stock on the grant date; (ii) expected volatility of our common stock price, (iii) the periods of time over which employees and non-employee directors are expected to hold their options prior to exercise (expected term), (iv) expected dividend yield on our common stock, and (v) risk-free interest rates.

The assumptions for expected volatility and the expected term of stock options used in computing the fair value of option awards reflect our best estimates but involve uncertainties related to market and other conditions, many of which are outside of our control. Changes in any of these assumptions may materially affect the fair value of stock options granted and the amount of stock-based compensation recognized in future periods.

**Accounting Pronouncements Recently Adopted; Recent Accounting Pronouncements Not Yet Adopted**

Please refer to Note 2 of Notes to Financial Statements, *Summary of Significant Accounting Policies*, in this Annual Report on Form 10-K.

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

***Interest Rate Risk***

We invest a majority of our cash reserves in a variety of available-for-sale marketable securities, including investment-grade debt instruments, principally corporate bonds, commercial paper, municipal bonds and direct obligations of the U.S. government and U.S. government-sponsored entities, and in cash equivalents. See Note 3 of Notes to Financial Statements, *Available-for-Sale Marketable Securities*, in this Annual Report on Form 10-K for details about our available-for-sale marketable securities.

As of December 31, 2019, we had invested $199.9 million of our cash reserves in such marketable securities. Those marketable securities include $199.9 million of investment grade debt instruments with a yield of approximately 2.08% and maturities through December 2021. As of December 31, 2018, we had invested $167.7 million of our cash reserves in such marketable securities. Those marketable securities include $167.7 million of investment grade debt instruments with a yield of approximately 2.64% and maturities through November 2020.

We maintain an investment portfolio in accordance with our investment policy, which includes guidelines on acceptable investment securities, minimum credit quality, maturity parameters, and concentration and diversification. The primary objectives of our investment policy are to preserve principal, maintain proper liquidity and to meet operating needs. Our investments are subject to interest rate risk and will decrease in value if market interest rates increase. However, due to the conservative nature of our investments and relatively short duration, interest rate risk is mitigated.

Duration is a sensitivity measure that can be used to approximate the change in the fair value of a security that will result from a change in interest rates. Applying the duration model, a hypothetical 1% increase in interest rates as of December 31, 2019 and 2018, would have resulted in immaterial decreases in the fair values of our portfolio of marketable securities at those dates. We do not currently use interest rate derivative instruments to manage exposure to interest rate changes.

***Credit Quality Risk***

Although our investments are subject to credit risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or type of investment. Nonetheless, deterioration of the credit quality of an investment security subsequent to purchase may subject us to the risk of not being able to recover the full principal value of the security.

**Item 8.** ***Financial Statements and Supplementary Data.***

**Cara Therapeutics, Inc.**
**INDEX TO FINANCIAL STATEMENTS**

## Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Cara Therapeutics, Inc.

**Opinion on the Financial Statements**

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

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 27, 2020 expressed an unqualified opinion thereon.

**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 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. 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.

**Critical Audit Matter**

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

***Revenue Recognition***

*Description of the Matter*

As discussed in Notes 1 and 2 to the financial statements, the Company earns its revenue from an agreement to license its intellectual property and perform related research and development services. The Company recognizes revenue over the period that the research and development services are performed and measures its progress toward completion based on the research and development costs incurred to date in proportion to the total research and development costs expected to be incurred to complete the clinical trials associated with the license agreement.

Auditing revenue recognition is complex and judgmental due to the variability and uncertainty associated with the Company's assessment of the total estimated research and development costs to be incurred in completing its obligations. Changes in this estimate would have a significant effect on the amount of revenue recognized in the period.

| | |
|---|---|
| *How We Addressed the Matter in Our Audit* | We obtained an understanding, evaluated the design, and tested the operating effectiveness of controls that address the risks of a material revenue misstatement, including management's review controls over the estimate of costs to complete ongoing clinical trials and controls over the completeness and accuracy of costs incurred to date.<br><br>To test the amount of revenue recognized in the financial statements our audit procedures included, among others, testing the Company's estimate of total costs to be incurred under the applicable clinical trials and confirming costs incurred through December 31, 2019 with clinical research organizations performing the services. We tested the estimate of total costs to be incurred by obtaining supporting agreements with the clinical research organizations conducting the trials and discussing progress to date and estimated future costs with the Company's clinical trial managers. We also compared the costs incurred to date to supporting documents from third parties and recalculated the Company's progress to date and the amount of revenue recognized. |

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2006.

Stamford, Connecticut

February 27, 2020

**Report of Independent Registered Public Accounting Firm**

To the Shareholders and the Board of Directors of Cara Therapeutics, Inc.

**Opinion on Internal Control Over Financial Reporting**

We have audited Cara Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Cara Therapeutics, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the balance sheets of the Company as of December 31, 2019 and 2018, the related statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2019, and the related notes and our report dated February 27, 2020 expressed an unqualified opinion thereon.

**Basis for Opinion**

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

**Definition and Limitations of Internal Control Over Financial Reporting**

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Stamford, Connecticut
February 27, 2020

**CARA THERAPEUTICS, INC.**

**BALANCE SHEETS**
**(amounts in thousands, except share and per share data)**

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 18,305 | $ 15,081 |
| Marketable securities | 136,701 | 146,302 |
| Income tax receivable | 816 | 664 |
| Other receivables | 971 | 926 |
| Prepaid expenses | 8,863 | 4,805 |
| Restricted cash, current | — | 361 |
| Total current assets | 165,656 | 168,139 |
| Operating lease right-of-use asset | 3,036 | — |
| Marketable securities, non-current | 63,159 | 21,396 |
| Property and equipment, net | 700 | 880 |
| Restricted cash | 408 | 408 |
| Total assets | $ 232,959 | $ 190,823 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable and accrued expenses | $ 19,665 | $ 13,622 |
| Operating lease liability, current | 967 | — |
| Current portion of deferred revenue | 22,262 | 26,825 |
| Total current liabilities | 42,894 | 40,447 |
| | | |
| Operating lease liability, non-current | 3,352 | — |
| Deferred revenue, non-current | — | 15,184 |
| Deferred lease obligation | — | 1,562 |
| Commitments and contingencies (Note 17) | — | — |
| Stockholders' equity: | | |
| Preferred stock; $0.001 par value; 5,000,000 shares authorized at December 31, 2019 and December 31, 2018, zero shares issued and outstanding at December 31, 2019 and December 31, 2018 | — | — |
| Common stock; $0.001 par value; 100,000,000 shares authorized at December 31, 2019 and December 31, 2018, 46,720,225 shares and 39,547,558 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively | 47 | 39 |
| Additional paid-in capital | 587,223 | 428,059 |
| Accumulated deficit | (400,727) | (294,354) |
| Accumulated other comprehensive income (loss) | 170 | (114) |
| Total stockholders' equity | 186,713 | 133,630 |
| Total liabilities and stockholders' equity | $ 232,959 | $ 190,823 |

See Notes to Financial Statements.

**CARA THERAPEUTICS, INC.**

**STATEMENTS OF COMPREHENSIVE LOSS**
**(amounts in thousands, except share and per share data)**

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Revenue: | | | |
| License and milestone fees | $ 19,746 | $ 13,436 | $ 530 |
| Collaborative revenue | — | — | 313 |
| Clinical compound revenue | 140 | 33 | 68 |
| Total revenue | 19,886 | 13,469 | 911 |
| Operating expenses: | | | |
| Research and development | 113,820 | 75,531 | 48,524 |
| General and administrative | 17,745 | 15,320 | 11,872 |
| Total operating expenses | 131,565 | 90,851 | 60,396 |
| Operating loss | (111,679) | (77,382) | (59,485) |
| Other income | 4,490 | 2,980 | 1,156 |
| Loss before benefit from income taxes | (107,189) | (74,402) | (58,329) |
| Benefit from income taxes | 816 | 389 | 204 |
| Net loss | $ (106,373) | $ (74,013) | $ (58,125) |
| Net loss per share: | | | |
| Basic and Diluted | $ (2.49) | $ (2.06) | $ (1.86) |
| Weighted average shares: | | | |
| Basic and Diluted | 42,669,333 | 35,892,786 | 31,202,842 |
| Other comprehensive income (loss), net of tax of $0: | | | |
| Change in unrealized gains (losses) on available-for-sale marketable securities | 284 | (44) | (73) |
| Total comprehensive loss | $ (106,089) | $ (74,057) | $ (58,198) |

See Notes to Financial Statements.

## CARA THERAPEUTICS, INC.

## STATEMENTS OF STOCKHOLDERS' EQUITY
## (amounts in thousands, except share and per share data)

| | Common Stock | | Additional Paid-in Capital | Accumulated Deficit | Accumulated Other Comprehensive Income (Loss) | Total Stockholders' Equity |
|---|---|---|---|---|---|---|
| | Shares | Amount | | | | |
| Balance at December 31, 2016 | 27,296,863 | $ 27 | $ 212,866 | $ (162,171) | $ 3 | $ 50,725 |
| Sale of common stock in a follow-on public offering ($18.00 per share), net of underwriting discounts and commissions and offering expenses of $5,891 | 5,117,500 | 5 | 86,219 | — | — | 86,224 |
| Stock-based compensation expense | — | — | 5,793 | — | — | 5,793 |
| Modification of equity awards | — | — | 537 | — | — | 537 |
| Shares issued upon exercise of stock options | 247,892 | 1 | 1,698 | — | — | 1,699 |
| Cumulative effect adjustment upon adoption of ASU 2016-09 | — | — | 45 | (45) | — | — |
| Net loss | — | — | — | (58,125) | — | (58,125) |
| Other comprehensive loss | — | — | — | — | (73) | (73) |
| Balance at December 31, 2017 | 32,662,255 | 33 | 307,158 | (220,341) | (70) | 86,780 |
| Sale of common stock under license agreement | 1,174,827 | 1 | 14,555 | — | — | 14,556 |
| Sale of common stock in a follow-on public offering ($19.00 per share), net of underwriting discounts and commissions and offering expenses of $6,262 | 5,175,000 | 5 | 92,058 | — | — | 92,063 |
| Stock-based compensation expense | — | — | 7,785 | — | — | 7,785 |
| Modification of equity awards | — | — | 616 | — | — | 616 |
| Shares issued upon vesting of restricted stock units | 83,791 | — | 1,693 | — | — | 1,693 |
| Shares issued upon exercise of stock options | 451,685 | — | 4,194 | — | — | 4,194 |
| Net loss | — | — | — | (74,013) | — | (74,013) |
| Other comprehensive loss | — | — | — | — | (44) | (44) |
| Balance at December 31, 2018 | 39,547,558 | 39 | 428,059 | (294,354) | (114) | 133,630 |
| Sale of common stock in a follow-on public offering ($23.00 per share), net of underwriting discounts and commissions and offering expenses of $8,977 | 6,325,000 | 7 | 136,491 | — | — | 136,498 |
| Issuance of common stock upon entry into License Agreement with Enteris Biopharma, Inc. ($23.42 per share) | 170,793 | — | 4,000 | — | — | 4,000 |
| Stock-based compensation expense | — | — | 10,587 | — | — | 10,587 |
| Shares issued upon exercise of stock options | 555,847 | 1 | 6,105 | — | — | 6,106 |
| Shares issued upon vesting of executive restricted stock units | 110,832 | — | 1,784 | — | — | 1,784 |
| Shares issued for consulting services | 10,195 | — | 197 | — | — | 197 |
| Net loss | — | — | — | (106,373) | — | (106,373) |
| Other comprehensive income | — | — | — | — | 284 | 284 |
| Balance at December 31, 2019 | 46,720,225 | $ 47 | $ 587,223 | $ (400,727) | $ 170 | $ 186,713 |

See Notes to Financial Statements.

**CARA THERAPEUTICS, INC.**

**STATEMENTS OF CASH FLOWS**
**(in thousands)**

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| **Operating activities** | | | |
| Net loss | $ (106,373) | $ (74,013) | $ (58,125) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Stock-based compensation expense | 12,568 | 9,478 | 5,793 |
| Modification of equity awards | — | 616 | 537 |
| Depreciation and amortization | 198 | 370 | 495 |
| Amortization expense component of lease expense | 601 | — | — |
| Noncash expense related to oral formulation license agreement | 4,000 | — | — |
| Accretion of available-for-sale marketable securities | (1,381) | (1,820) | (582) |
| Realized loss (gain) on sale of available-for-sale marketable securities | — | 5 | (5) |
| Realized gain on sale of property and equipment | — | — | (41) |
| Deferred rent costs | — | (156) | 148 |
| Deferred revenue | (19,747) | 42,009 | — |
| Changes in operating assets and liabilities: | | | |
| Income tax receivable | (152) | 67 | 121 |
| Other receivables | (45) | (803) | (36) |
| Prepaid expenses | (4,058) | (3,170) | (105) |
| Accounts payable and accrued expenses | 6,043 | 5,116 | (3,027) |
| Operating lease liability | (879) | — | — |
| Net cash used in operating activities | (109,225) | (22,301) | (54,827) |
| **Investing activities** | | | |
| Proceeds from maturities of available-for-sale marketable securities | 253,584 | 175,300 | 82,156 |
| Proceeds from redemptions of available-for-sale marketable securities, at par | 2,000 | — | — |
| Proceeds from sale of available-for-sale marketable securities | — | 79,808 | 8,755 |
| Purchases of available-for-sale marketable securities | (286,082) | (337,854) | (127,394) |
| Purchases of property and equipment | (18) | (73) | (58) |
| Proceeds from sale of property and equipment | — | — | 41 |
| Net cash used in investing activities | (30,516) | (82,819) | (36,500) |
| **Financing activities** | | | |
| Proceeds from the sale of common stock in a follow-on public offering, net of issuance costs | 136,498 | 92,063 | 86,224 |
| Proceeds from the sale of common stock under license agreement | — | 14,556 | — |
| Proceeds from the exercise of stock options | 6,106 | 4,194 | 1,699 |
| Net cash provided by financing activities | 142,604 | 110,813 | 87,923 |
| Net increase (decrease) in cash, cash equivalents and restricted cash | 2,863 | 5,693 | (3,404) |
| Cash, cash equivalents and restricted cash at beginning of period | 15,850 | 10,157 | 13,561 |
| Cash, cash equivalents and restricted cash at end of period | $ 18,713 | $ 15,850 | $ 10,157 |
| **Noncash investing and financing activities** | | | |
| Shares of common stock issued in connection with oral formulation license agreement | $ 4,000 | $ — | $ — |
| Shares of common stock issued in exchange for consulting services | 197 | — | — |

See Notes to Financial Statements.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

## 1. Business

Cara Therapeutics, Inc., or the Company, is a clinical-stage biopharmaceutical corporation formed on July 2, 2004. The Company is focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors. The Company's primary activities to date have been organizing and staffing the Company, developing its product candidates and raising capital.

As of December 31, 2019, the Company has raised aggregate net proceeds of approximately $519,600 from several rounds of equity financing, including its initial public offering, or IPO, which closed in February 2014 and four follow-on public offerings of common stock, which closed in July 2019, July 2018, April 2017 and August 2015, respectively, and the issuance of convertible preferred stock and debt prior to the IPO. The Company had also received approximately $89,000 under its license agreements for CR845/difelikefalin, primarily with Vifor Fresenius Medical Care Renal Pharma Ltd., or VFMCRP, Maruishi Pharmaceutical Co. Ltd., or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or CKDP, and an earlier product candidate for which development efforts ceased in 2007. Additionally, in May 2018, the Company received net proceeds of $14,556 from the issuance and sale of 1,174,827 shares of the Company's common stock to Vifor (International) Ltd., or Vifor, in connection with the Company's license agreement with VFMCRP (see Note 11, *Collaboration and Licensing Agreements*).

As of December 31, 2019, the Company had unrestricted cash and cash equivalents and marketable securities of $218,165 and an accumulated deficit of $400,727. The Company has incurred substantial net losses and negative cash flows from operating activities in nearly every fiscal period since inception and expects this trend to continue for the foreseeable future. The Company recognized a net loss of $106,373 and had net cash used in operating activities of $109,225 for the year ended December 31, 2019.

The Company is subject to risks common to other life science companies including, but not limited to, uncertainty of product development and commercialization, lack of marketing and sales history, development by its competitors of new technological innovations, dependence on key personnel, market acceptance of products, product liability, protection of proprietary technology, ability to raise additional financing, and compliance with Food and Drug Administration, or FDA, and other government regulations. If the Company does not successfully commercialize any of its product candidates, it will be unable to generate recurring product revenue or achieve profitability.

## 2. Summary of Significant Accounting Policies

### *Basis of Presentation*

Certain amounts in the prior years' financial statements have been reclassified to conform to the current-year presentation due to the adoption of Accounting Standards Update, or ASU, No. 2016-18, *Statement of Cash Flows (Topic 230), Restricted Cash*, or ASU 2016-18, on January 1, 2018.

### *Use of Estimates*

The preparation of financial statements in conformity with generally-accepted accounting principles in the United States or GAAP, requires the Company to make estimates and assumptions that affect the reported amounts of assets and liabilities, and disclosure of contingent assets and liabilities, as of the date of the financial statements as well as the reported amounts of revenues and expenses during the reporting period. Actual results could differ materially from the Company's estimates and assumptions. Estimates include the fair value of marketable securities that are classified as level 2 of the fair value hierarchy, useful lives of fixed assets, the periods over which certain revenues will be recognized, including licensing and collaborative revenue recognized from non-refundable up-front and milestone payments, the determination of prepaid research and development, or R&D, clinical costs and accrued research projects,

the amount of non-cash compensation costs related to share-based payments to employees and non-employees and the periods over which those costs are expensed, the incremental borrowing rate used in lease calculations and the likelihood of realization of deferred tax assets.

***Concentrations of Credit Risk***

Financial instruments, which potentially subject the Company to significant concentrations of credit risk consist primarily of cash equivalents and marketable securities. The Company invests its cash reserves in money market funds or high-quality marketable securities in accordance with its investment policy. The stated objectives of its investment policy are to preserve capital, provide liquidity consistent with forecasted cash flow requirements, maintain appropriate diversification and generate returns relative to these investment objectives and prevailing market conditions. The Company's investment policy includes guidelines on acceptable investment securities, limits interest-bearing security investments to certain types of debt and money market instruments issued by the U.S. government and institutions with investment grade credit ratings and places restrictions on maturities and concentration by asset class and issuer. The Company's cash and cash equivalents and marketable securities are held by four major financial institutions. In accordance with the Company's policies, the Company monitors exposure with its counterparties. The Company also maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held.

***Cash and Cash Equivalents***

Cash and cash equivalents include cash on hand, demand deposits, deposits with banks and highly liquid money market funds with holdings of cash and other investments with original maturities of three months or less.

***Marketable Securities***

The Company deems certain of its investments to be marketable securities if the investment, or in the case of money market funds, the securities underlying the money market fund, meet the definition of a debt security in Accounting Standards Codification, or ASC, section 320-10-20. The Company considers its marketable securities to be available-for-sale and, accordingly, these investments are recorded at fair value with unrealized gains and losses recorded in Accumulated other comprehensive income (loss), or AOCI, as a separate component of stockholders' equity. Available-for-sale marketable securities are reported as Marketable securities, current and Marketable Securities, noncurrent in the Balance Sheets. Other income includes interest and dividends, accretion/amortization of discounts/premiums and realized gains and losses on sales of securities and other-than-temporary impairment, or OTTI, declines in the fair value of securities, if any. The cost of securities sold is based on the specific identification method.

The Company reviews its available-for-sale marketable securities for OTTI declines in fair value below its cost basis each quarter and whenever events or changes in circumstances indicate that the cost basis of an asset may not be recoverable. This evaluation is based on a number of factors, including the length of time and the extent to which the fair value has been below its cost basis and adverse conditions related specifically to the security, including any changes to the credit rating of the security, and the intent to sell, or whether the Company will more likely than not be required to sell, the security before recovery of its amortized cost basis. The Company's assessment of whether a security is other-than-temporarily impaired could change in the future due to new developments or changes in assumptions related to any particular security.

If a decline in the fair value of an available-for-sale marketable debt security in the Company's investment portfolio is deemed to be other-than-temporary, the Company writes down the security to its current fair value. If the Company intends to sell the security or it is more likely than not that the Company will be forced to sell the security

before recovery of the amortized cost of the security, the loss is recognized in net income. Otherwise, the loss is separated into a portion representing a credit loss, which is recorded in net income, and the remainder is recorded in Other comprehensive income, or OCI, net of taxes. See Note 2, *Recent Accounting Pronouncements Not Yet Adopted*, Note 3, *Available-for-Sale Marketable Securities*, and Note 10, *Fair Value Measurements*.

***Fair Value of Financial Instruments***

The Company applies fair value accounting for all financial assets and liabilities that are recognized or disclosed at fair value in the financial statements on a recurring basis. The Company defines fair value as the price that would be received from selling an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. When determining the fair value measurements for assets and liabilities which are required to be recorded at fair value, the Company considers the principal or most advantageous market in which it would transact and the market-based risk measurements or assumptions that market participants would use in pricing the asset or liability, such as risks inherent in valuation techniques, transfer restrictions and credit risks.

The Company's financial instruments consist of cash, cash equivalents, available-for-sale marketable securities, prepaid expenses, restricted cash, accounts payable and accrued liabilities. The fair values of cash, cash equivalents, prepaid expenses, restricted cash, accounts payable and accrued liabilities approximate their carrying values due to the short-term nature of these financial instruments. Available-for-sale marketable securities are reported on the Company's Balance Sheets as Marketable Securities at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by third-party pricing services, as described below.

Current accounting guidance defines fair value, establishes a framework for measuring fair value in accordance with ASC section 820, 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 the Company's assumptions about the inputs that market participants would use in pricing the asset or liability and are developed based on the best information available in the circumstances.

The Company classifies its investments in a fair value hierarchy that is intended to increase consistency and comparability in fair value measurements and related disclosures. The fair value hierarchy is divided into three levels based on the source of inputs as follows:

- 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 Company records transfers between levels in the hierarchy by assuming that the transfer occurred at the end of the quarter or year-to-date period.

*Valuation Techniques - Level 2 Inputs*

The Company estimates the fair values of its financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, commercial paper

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

and municipal bonds, by taking into consideration valuations obtained from third-party pricing services. The pricing services use industry standard valuation models, including both income- and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker/dealer quotes on the same or similar securities, benchmark yields, issuer credit spreads, benchmark securities, and other observable inputs. The Company obtains a single price for each financial instrument and does not adjust the prices obtained from the pricing service.

The Company validates the prices provided by its third-party pricing services by reviewing their pricing methods, obtaining market values from other pricing sources and comparing them to the share prices presented by the third-party pricing services. After completing its validation procedures, the Company did not adjust or override any fair value measurements provided by its pricing services as of December 31, 2019 or December 31, 2018.

***Property and Equipment***

Property and equipment (consisting of computer, office and laboratory equipment, furniture and fixtures and leasehold improvements) are stated at cost, net of accumulated depreciation and amortization of leasehold improvements. Depreciation and amortization are calculated using the straight-line method over the estimated useful lives of the respective assets. Leasehold improvements are amortized over the lesser of their useful lives or the life of the lease.

| Asset Category | Useful Lives |
|---|---|
| Computer and office equipment | 5 years |
| Short-term laboratory equipment | 2 years |
| Furniture and fixtures | 7 years |
| Leasehold improvements | lesser of useful life of asset or life of lease (Stamford - 7 years) |

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 property and equipment 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.

***Revenue Recognition***

On January 1, 2018, the Company adopted Accounting Standards Update, or ASU, 2014-09, *Revenue from Contracts with Customers (Topic 606)*, or ASC 606, as amended by ASU 2016-08, 2016-10, 2016-12 and 2016-20 using the full retrospective method. Under ASC 606, the Company recognizes revenue in an amount that reflects the consideration to which it expects to be entitled in exchange for the transfer of promised goods or services to customers. To determine revenue recognition for contracts with customers that are within the scope of ASC 606, the Company performs the following steps: (1) identifies the contract with the customer, (2) identifies the performance obligations in the contract, (3) determines the transaction price, (4) allocates the transaction price to the performance obligations in the contract, and (5) recognizes revenue when (or as) the entity satisfies a performance obligation. The Company has concluded that upon adoption of ASC 606, as amended, there was no impact on its results of operations, financial position or cash flows for any period presented from its only two revenue-related contracts, which were in effect at that time: the CKDP Agreement or the Maruishi Agreement (see Note 11, *Collaboration and Licensing Agreements* and Note 12, *Revenue Recognition)*.

The Company has entered into agreements to license its intellectual property, or IP, related to CR845/difelikefalin to develop, manufacture and/or commercialize drug products. These agreements typically contain multiple performance

obligations, including licenses of IP and R&D services. Payments to the Company under these agreements may include nonrefundable license fees, payments for research activities, payments based upon the achievement of certain milestones and royalties on any resulting net product sales.

The Company identifies agreements as contracts that create enforceable rights and obligations when the agreement is approved by the parties, identifies the rights of the parties and the payment terms, has commercial substance and it is probable that the Company will collect the consideration to which it will be entitled in exchange for the goods and services that will be transferred to the customer. The counterparty is considered to be a customer when it has contracted with the Company to obtain goods and services that are the output of the Company's ordinary activities (i.e., development of pharmaceutical products) in exchange for consideration.

A performance obligation is a promise to transfer distinct goods or services to a customer. Performance obligations that are both capable of being distinct and distinct within the context of the contract are considered to be separate performance obligations. Performance obligations are capable of being distinct if the counterparty is able to benefit from the good or service on its own or together with other resources that are readily available to it. Performance obligations are distinct within the context of the contract when each performance obligation is separately identifiable from each other; i.e., the Company is not using the goods or services as inputs to produce or deliver the combined output or outputs specified by the customer; one or more of the goods or services does not significantly modify or customize one of the other goods or services in the contract; and goods or services are not highly interdependent or not highly interrelated. Performance obligations that are not distinct are accounted for as a single performance obligation over the period that goods or services are transferred to the customer. The determination of whether performance obligations in a contract are distinct may require significant judgment.

The transaction price is the amount of consideration that the Company expects to be entitled to in exchange for transferring promised goods or services to the customer based on the contract terms at inception of a contract. There is a constraint on inclusion of variable consideration related to licenses of IP, such as milestone payments or sales-based royalty payments, in the transaction price if there is uncertainty at inception of the contract as to whether such consideration will be recognized in the future because it is probable that there will be a significant reversal of revenue in the future when the uncertainty is resolved. The determination of whether or not it is probable that a significant reversal of revenue will occur in the future depends on the likelihood and magnitude of the reversal. Factors that could increase the likelihood or magnitude of a reversal of revenue include (a) the susceptibility of the amount of consideration to factors outside the entity's influence, such as the outcome of clinical trials, the timing of initiation of clinical trials by the counterparty and the approval of drug product candidates by regulatory agencies, (b) situations in which the uncertainty is not expected to be resolved for a long period of time, and (c) level of the Company's experience in the field. When it becomes probable that events will occur, for which variable consideration was constrained at inception of the contract, the Company allocates the related consideration to the separate performance obligations in the same manner as described below.

At inception of a contract, the Company allocates the transaction price to the distinct performance obligations based upon their relative standalone selling prices. Standalone selling price is the price at which an entity would sell a promised good or service separately to a customer. The best evidence of standalone selling price is an observable price of a good or service when sold separately by an entity in similar circumstances to similar customers. Since the Company typically does not have such evidence, it estimates standalone selling price so that the amount that is allocated to each performance obligation equals the amount that the Company expects to receive for transferring goods or services. The methods that the Company uses to make such estimates include (1) the adjusted market assessment approach, under which the Company forecasts and analyzes CR845/difelikefalin in the appropriate market, the phase of clinical development as well as considering recent similar license arrangements within the same phase of clinical development, therapeutic area, type of agreement, etc. and (2) the expected cost of satisfying the performance obligations plus a margin, or the expected cost plus a margin approach.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

The Company recognizes revenue when, or as, it satisfies a performance obligation by transferring a promised good or service to a customer and the customer obtains control of the good or service. Revenue related to the grant of a license that is a distinct performance obligation and that is deemed to be functional IP is recognized at the point in time that the Company has the right to payment for the license, the customer has legal title to the license and can direct the use of the license (for example, to grant sublicenses), the customer has the significant risks and rewards of ownership of the license and the customer has accepted the asset (license) by signing the license agreement.

Recognition of revenue related to R&D services that are a distinct performance obligation or that are combined with granting of a license as a single performance obligation is deferred at inception of a contract and is recognized as those services are performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation.

Milestone payments are considered to be variable consideration and are not included in the transaction price at inception of the contract if it is uncertain that the milestone will be achieved. Rather, when it becomes probable that the milestone will be achieved and, therefore, there will not be a significant reversal of revenue in future periods, the respective amount to be earned is included in the transaction price, allocated to the distinct performance obligations based on their relative standalone selling price and recognized as revenue, as described above. Sales milestones and sales-based royalty payments related to a license of IP are recognized as revenue when the respective sales occur.

***Research and Development Expenses***

Research and development, or R&D, costs are charged to expense as incurred. Costs incurred under agreements with third parties are charged to expense as incurred in accordance with the specific contractual performance terms of such agreements. R&D expenses include, among other costs, compensation and other personnel-related costs, including consultant costs, and costs to conduct clinical trials using clinical research organizations, or CRO's, which include upfront, milestone and monthly expenses as well as reimbursement for pass through costs. The amount of clinical trial expense recognized in any period varies depending on the duration and progress of each clinical trial, including the required level of patient enrollment, the rate at which patients actually enroll in and drop-out of the clinical trial, and the number of sites involved in the trial as well as the activities to be performed by the sites each period. R&D costs also include costs to manufacture product candidates and clinical supplies, laboratory supplies costs, facility-related costs and stock-based compensation for R&D personnel. Non-refundable R&D advance payments are deferred and capitalized as prepaid R&D expense. The capitalized amounts are expensed as the related goods are delivered or services are performed. As of December 31, 2019 and 2018, the Company recorded $8,498 and $4,377 as prepaid R&D expense, respectively.

***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*, which prescribes a comprehensive model for how a company should recognize, measure, present and disclose in its financial statements uncertain tax positions that it has taken or expects to take on a tax return. There were no material uncertain tax positions taken as of 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.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

***Stock-Based Compensation***

The Company grants stock options to employees, non-employee members of the Company's Board of Directors and non-employee consultants as compensation for services performed. Employee and non-employee members of the Board of Directors' awards of stock-based compensation are accounted for in accordance with ASC 718, *Compensation - Stock Compensation*, or ASC 718. ASC 718 requires all share-based payments to employees and non-employee directors, including grants of stock options, to be recognized in the Statements of Comprehensive Loss based on their grant date fair values. The grant date fair value of stock options is estimated using the Black-Scholes option valuation model.

Using this model, fair value is calculated based on assumptions with respect to (i) the fair value or market price of the Company's common stock on the grant date; (ii) expected volatility of the Company's common stock price, (iii) the periods of time over which employees and members of the Company's Board of Directors are expected to hold their options prior to exercise (expected term), (iv) expected dividend yield on the Company's common stock, and (v) risk-free interest rates.

The Company's common stock has been traded on a public exchange only since January 31, 2014. Since that time, exercises of stock options have been limited due to various factors, including fluctuations in the Company's stock price to below the exercise prices of awards and blackout periods during which exercises are not allowed, among others. Therefore, the Company believes that as of December 31, 2019, it does not have sufficient company-specific information available to determine the expected term based on its historical data. As a result, the expected term of stock options granted to employees and members of the Company's Board of Directors is determined using the average of the vesting period and term (6.25 years), an accepted method for the Company's option grants under the SEC's Staff Accounting Bulletin No. 110, *Share-Based Payment.*

During the period from January 31, 2014 to December 31, 2018, the Company's stock had not traded on a public exchange for a sufficient period of time to approximate its expected term (as noted above). Therefore, the Company calculated the volatility for stock options granted using an analysis of guideline companies in accordance with ASC 718. Volatility calculated in this manner had been in the range of 83% - 93% and 75% - 85% for stock options granted during the years ended December 31, 2018 and 2017, respectively.

Beginning on January 1, 2019, the Company determined that it had sufficient company-specific trading activity of its common stock available to use that activity exclusively to calculate the volatility of the Company's common stock. Volatility calculated in this manner was in the range of 71% - 75% for the period of January 31, 2014 to each respective grant date within the year ended December 31, 2019. Volatility of the Company's common stock from January 31, 2014 to December 31, 2018 and 2017 was 75% and 79%, respectively.

The expected dividend yield is zero as the Company has never paid dividends and does not currently anticipate paying any in the foreseeable future. Risk-free interest rates are based on quoted U.S. Treasury rates for securities with maturities approximating the option's expected term.

As of January 1, 2017, the Company adopted ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, or ASU 2016-09. On the date of adoption of ASU 2016-09, the Company began to account for forfeitures of unvested stock options as they occur rather than estimate forfeiture rates that were applied to unvested stock option awards, as under the previous accounting guidance. Accordingly, on the date of adoption, the Company recorded a cumulative effect adjustment to stockholders' equity of $45 thousand for all stock option awards that were unvested as of that date.

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Prior to January 1, 2019, the Company accounted for stock options granted to non-employee consultants under ASC 505-50, *Equity-Based Payments to Non-Employees*. As such, the Company estimated the fair value of each option to non-employees using the Black-Scholes model, with the expected term of stock options granted to non-employees initially equal to the options' maximum contractual life of ten years, at issuance. On each subsequent reporting date until performance was complete, the Company revalued all outstanding options granted to non-employee consultants during the vesting period of each tranche. Under ASC 505-50, upon re-measurement of each award, income or expense was recognized during its vesting term.

On January 1, 2019, the Company adopted ASU 2018-07, *Compensation – Stock Compensation (Topic 718), Improvements to Non-employee Share-Based Payment Accounting*, or ASU 2018-07, which expanded the scope of ASC 718 to include share-based payment transactions for acquiring goods and services from non-employees. As a result, the fair value of all outstanding unvested stock options that had been granted to non-employees as of January 1, 2019 was remeasured on that date. The adoption of ASU 2018-07 did not have a material effect on the Company's results of operations, financial position or cash flows because grants of stock options to nonemployees have been insignificant.

For all share-based payments granted to employees and non-employees, compensation cost relating to awards with service-based graded vesting schedules is recognized using the straight-line method over the requisite service period.

***Income (Loss) Per Share***

The Company computes basic net income (loss) per share by dividing net income (loss) by the weighted average number of shares of common stock outstanding. Diluted net income per share includes the potential dilutive effect of common stock equivalents as if such securities were exercised during the period, when the effect is dilutive. Common stock equivalents may include outstanding stock options, which are included under the treasury stock method when dilutive. For each of the years ended December 31, 2019, 2018 and 2017, the Company excluded the effects of potentially dilutive shares that were outstanding during those respective periods from the denominator as their inclusion would be anti-dilutive due to the Company's net losses during those periods.

***Segment Reporting***

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business as one operating segment, which includes all activities related to the discovery and development of novel therapeutics to treat serious medical conditions, including pruritus and pain.

***Leases***

Prior to January 1, 2019, the Company recognized rent expense for operating leases on a straight-line basis over the term of the lease, beginning on the date the Company took possession of the property. Rent expense included the base amounts stated in the lease agreement as well as the effect of reduced or free rent and rent escalations. At lease inception, the Company determined the lease term by assuming the exercise of those renewal options that are reasonably assured because of the significant economic penalty that exists for not exercising those options. The exercise of renewal options is at the Company's sole discretion. The expected lease term was one of the factors used to determine whether a lease was classified as operating or capital and was used to calculate the straight-line rent expense. The difference between the cash paid to the landlord and the amount recognized as rent expense on a straight-line basis was included in deferred rent and classified within long-term liabilities for the year ended December 31, 2018. Lease incentives made by landlords to or on behalf of the Company for leasehold improvements were recorded as deferred rent and classified as long-term liabilities for the year ended December 31, 2018. Deferred rent related to landlord incentives was amortized

using the straight-line method over the lease term as an offset to rent expense for the years ended December 31, 2018 and 2017, respectively.

On January 1, 2019, the Company adopted ASC 842, *Leases*, or ASC 842, under which it elected not to adjust prior comparative periods, which are reported under ASC 840. In addition, the Company elected to adopt both the practical expedient to use hindsight when determining the lease term and the package of practical expedients available under ASC 842, including:

- No re-evaluation of whether a contract is or contains a lease (embedded lease);
- Lease classification is grandfathered
- No reassessment of initial direct costs

Upon adoption of ASC 842, the Company had only one lease, the Stamford Lease (see Note 17, *Commitments and Contingencies: Leases*), which is included in operating lease right-of-use asset, or ROU asset, operating lease liability – current and operating lease liability – non-current in the Company's Balance Sheet.

In general, the Company determines if a contract, at its inception, is a lease or contains a lease based on whether the contract conveys the right to control the use of identified property, plant, or equipment (an identified asset) for a period of time in exchange for consideration. To determine whether a contract conveys the right to control the use of an identified asset for a period of time, the Company assesses whether, throughout the period of use, it has both the right to obtain substantially all of the economic benefits from use of the identified asset, and the right to direct the use of the identified asset. Both of these criteria are met by the Stamford Lease.

Under ASC 842, the Company determines the amount of the operating lease liability based on the present value of the future minimum lease payments over the remaining lease term. The amount of the operating lease ROU asset is equal to the amount of the lease liability, less accrued rent and lease incentives received from the landlord. Initial direct costs were deemed to be immaterial.

Since the Stamford Lease does not provide an implicit interest rate, the Company used an annual incremental borrowing rate of 7% based on the information available at the date of adoption for the purpose of determining the lease liability during the term of the lease.

As noted above, upon adoption of ASC 842, the Company used hindsight in determining the term of the Stamford Lease. Although the Stamford Lease is renewable for one five-year term, upon inception of the lease the renewal term was not included in the lease term since it was not reasonably certain that the Company will exercise that option. Accordingly, the lease term of the Stamford Lease was not adjusted upon adoption of ASC 842 to determine the operating lease ROU asset and operating lease liability.

The Stamford Lease contains both a lease and non-lease component which are accounted for separately. The Company allocates the consideration to the lease and the non-lease component on a relative standalone price basis. Lease expense under ASC 842 is recognized on a straight-line basis over the lease term in the Statement of Comprehensive Loss.

There was no cumulative effect adjustment as a result of the adoption of ASC 842 on January 1, 2019, which reflects the difference between the amount of lease expense under ASC 842 that would have been recognized from inception of the Stamford Lease through December 31, 2018 and the amount of rent expense actually recognized under ASC 840 during that same period.

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***Litigation Reserves***

From time to time, the Company may become subject to arbitration, litigation or claims arising in the ordinary course of its business. Accruals are recorded when it is probable that a liability has been incurred and the amount of the liability can be reasonably estimated. The Company reviews these reserves at least quarterly and adjusts these reserves to reflect current law, progress of each case, opinions and views of legal counsel and other advisers, the Company's experience in similar matters and intended response to the litigation. The Company expenses amounts for administering or litigating claims as incurred. Accruals for legal proceedings, if any, are included in Accounts payable and accrued expenses in the Balance Sheets.

***Accounting Pronouncements Recently Adopted***

The Company adopted ASC 842 and ASU 2018-07 on January 1, 2019. See Note 2, *Summary of Significant Accounting Policies: Leases* and *Stock-Based Compensation.*

***Recent Accounting Pronouncements Not Yet Adopted***

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740)*, or ASU 2019-12, which removes specific exceptions to the general principles in Topic 740. ASU 2019-12 eliminates the need for an organization to analyze whether the following apply in a given period: i) exception to the incremental approach for intra-period tax allocation; ii) exceptions to accounting for basis differences when there are ownership changes in foreign investments; and iii) exception to the general methodology for calculating income taxes in an interim period when a year-to-date loss exceeds the anticipated loss. ASU 2019-12 also simplifies the accounting for income taxes for: i) franchise taxes that are partially based on income; ii) transactions with a government that result in a step up in the tax basis of goodwill; (iii) separate financial statements of legal entities that are not subject to tax; and iv) enacted changes in tax laws in interim periods. 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 the amendments is permitted. 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 and must adopt all the amendments in the same period. The amendments in ASU 2019-12 related to separate financial statements of legal entities that are not subject to tax should be applied on a retrospective basis for all periods presented. The amendments related to changes in ownership of foreign equity method investments or foreign subsidiaries should be applied on a modified retrospective basis through a cumulative-effect adjustment to retained earnings as of the beginning of the fiscal year of adoption. The amendments related to franchise taxes that are partially based on income should be applied on either a retrospective basis for all periods presented or a modified retrospective basis through a cumulative-effect adjustment to retained earnings as of the beginning of the fiscal year of adoption. All other amendments should be applied on a prospective basis. As such, the Company expects to adopt ASU 2019-12 on January 1, 2021 and is currently evaluating the effect it will have on its results of operations, financial position and cash flows.

In November 2019, the FASB issued ASU 2019-08, *Compensation – Stock Compensation (Topic 718) and Revenue from Contracts with Customers (Topic 606)*, or ASU 2019-08, which requires companies to measure and classify share-based payment awards granted to a customer by applying the guidance in Topic 718. The amount recorded as a reduction to the transaction price is required to be measured on the basis of the grant-date fair value of the share-based payment award in accordance with Topic 718. The grant date is the date at which a grantor (supplier) and a grantee (customer) reach a mutual understanding of the key terms and conditions of a share-based payment award. The classification and subsequent measurement of the award are subject to the guidance in Topic 718 unless the share-based payment award is subsequently modified and the grantee is no longer a customer. For entities that have adopted ASU 2018-07, the amendments in ASU 2019-08 are effective in fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. An entity may also early adopt the amendments in ASU 2019-08, but not before it

adopts the amendments in ASU 2018-07. The Company will adopt ASU 2019-08 on January 1, 2020 and determined that the adoption will not have a material effect on its results of operations, financial position or cash flows since the Company has not historically granted share-based payment awards to customers.

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*, or ASU 2018-18, which clarifies the interaction between Topic 808 and Topic 606 by (1) clarifying that certain transactions between collaborative arrangement participants should be accounted for under Topic 606; (2) adding unit-of-account guidance in Topic 808 to align with the guidance in Topic 606; and (3) clarifying presentation guidance for transactions with a collaborative arrangement participant that are not accounted for under Topic 606. ASU 2018-18 is effective for public business entities for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted, including adoption in any interim period. The Company will adopt ASU 2018-18 on January 1, 2020 and has determined that ASU 2018-18 will not have any effect on its financial position, results of operations or cash flows since all three of its collaboration and licensing agreements are accounted for under Topic 606 (see Note 11, *Collaboration and Licensing Agreements* and Note 12, *Revenue Recognition*).

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework – Changes to the Disclosure Requirements for Fair Value Measurement*, or ASU 2018-13, which modifies the disclosure requirements on fair value measurements in Topic 820 to remove the amount of and reasons for transfers between Level 1 and Level 2 of the fair value hierarchy, the policy for timing of transfers between levels, and the valuation processes for Level 3 fair value measurements. ASU 2018-13 also amends Topic 820 to clarify that the measurement uncertainty disclosure is to communicate information about the uncertainty in measurement as of the reporting date. ASU 2018-13 also requires additional disclosure for changes in unrealized gains and losses for the period included in other comprehensive income for recurring Level 3 fair value measurements held at the end of the reporting period as well as the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements. ASU 2018-13 is effective for all entities for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2019. The amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements, and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all periods presented upon their effective date. Early adoption is permitted upon issuance of ASU 2018-13. The Company will adopt ASU 2018-13, as applicable, on January 1, 2020. The Company determined that the adoption will not have a material effect on its results of operations, financial position or cash flows.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326), Measurement of Credit Losses on Financial Instruments*, or ASU 2016-13, which replaces the incurred loss impairment methodology in current GAAP, that delays recognition of a credit loss until it is probable that such loss has been incurred, with a methodology that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to inform credit loss estimates. ASU 2016-13 modifies the other-than-temporary impairment model for available-for-sale debt securities by requiring (1) estimating expected credit losses only when the fair value is below the amortized cost of the asset; (2) recording a credit loss without regard to the length of time a security has been in an unrealized loss position; (3) limiting the measurement of the credit loss to the difference between the security's amortized cost basis and its fair value and (4) presenting credit losses as an allowance rather than as a write-down, which will allow the Company to record reversals of credit losses in current period net income, a practice that is currently prohibited. In April and November 2019, respectively, codification improvements were issued to help clarify and correct certain portions of ASU 2016-13. ASU 2016-13 will be effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. The Company will adopt ASU 2016-13 on January 1, 2020 and believes ASU 2016-13 will primarily impact the Company's assessment of any potential impairment of its investments in debt securities, specifically its assessment of whether any portion of an unrealized loss

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in a given period relates to a credit loss. As a result, the Company will revise its internal controls and procedures as of January 1, 2020 to periodically assess whether any portion of an unrealized loss in a given period relates to a credit loss. As of December 31, 2019, the adoption of ASU 2016-13 is not expected to have a material impact on the Company's results of operations, financial position or cash flows.

### 3. Available-for-Sale Marketable Securities

As of December 31, 2019, and 2018, the Company's available-for-sale marketable securities consisted of debt securities issued by the U.S. Treasury, U.S. government-sponsored entities and investment grade institutions as well as municipal bonds.

The following tables summarize the Company's available-for-sale marketable securities by major type of security as of December 31, 2019, and 2018:

**As of December 31, 2019**

| Type of Security | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Estimated Fair Value |
|---|---|---|---|---|
| U.S. Treasury securities | $ 16,052 | $ 31 | $ (2) | $ 16,081 |
| U.S. government agency obligations | 25,803 | 14 | (1) | 25,816 |
| Corporate bonds | 115,788 | 125 | (23) | 115,890 |
| Commercial paper | 38,547 | 27 | (1) | 38,573 |
| Municipal bonds | 3,500 | — | — | 3,500 |
| Total available-for-sale marketable securities | $ 199,690 | $ 197 | $ (27) | $ 199,860 |

**As of December 31, 2018**

| Type of Security | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Estimated Fair Value |
|---|---|---|---|---|
| U.S. Treasury securities | $ 19,540 | $ — | $ (1) | $ 19,539 |
| U.S. government agency obligations | 17,860 | — | (1) | 17,859 |
| Corporate bonds | 75,999 | 5 | (94) | 75,910 |
| Commercial paper | 50,413 | — | (23) | 50,390 |
| Municipal bonds | 4,000 | — | — | 4,000 |
| Total available-for-sale marketable securities | $ 167,812 | $ 5 | $ (119) | $ 167,698 |

All available-for-sale marketable securities are classified as Marketable securities, current or Marketable Securities, non-current depending on the contractual maturity date of the individual available-for-sale security.

The Company classifies its marketable debt securities based on their contractual maturity dates. As of December 31, 2019, the Company's marketable debt securities mature at various dates through December 2021. The amortized cost and fair values of marketable debt securities by contractual maturity were as follows.

| Contractual maturity | As of December 31, 2019 Amortized Cost | As of December 31, 2019 Fair Value | As of December 31, 2018 Amortized Cost | As of December 31, 2018 Fair Value |
|---|---|---|---|---|
| Less than one year | $ 136,565 | $ 136,701 | $ 146,363 | 146,302 |
| One year to two years | 63,125 | 63,159 | 21,449 | 21,396 |
| Total | $ 199,690 | $ 199,860 | $ 167,812 | $ 167,698 |

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There were no sales of available-for-sale marketable securities during the year ended December 31, 2019. During the year ended December 31, 2018, the Company sold shares of its investments in available-for-sale marketable securities with a total fair value of $79,808. The cost of the available-for-sale marketable securities that were sold was determined by specific identification. The sales of the investments in available-for-sale marketable securities during the year ended December 31, 2018 resulted in realized losses of $(5).

The following tables show the fair value of the Company's available-for-sale marketable securities that have unrealized losses and that are deemed to be only temporarily impaired, aggregated by investment category and length of time that the individual investments have been in a continuous unrealized loss position.

| | Less than 12 Months | | 12 Months or Greater | | Total | |
|---|---|---|---|---|---|---|
| | Fair Value | Gross Unrealized Losses | Fair Value | Gross Unrealized Losses | Fair Value | Gross Unrealized Losses |
| U.S. Treasury securities | $ 3,185 | $ (2) | $ — | $ — | $ 3,185 | $ (2) |
| U.S. government agency obligations | 2,400 | (1) | — | — | 2,400 | (1) |
| Corporate bonds | 28,895 | (23) | — | — | 28,895 | (23) |
| Commercial paper | 4,264 | (1) | — | — | 4,264 | (1) |
| Total | $ 38,744 | $ (27) | $ — | $ — | $ 38,744 | $ (27) |

| | Less than 12 Months | | 12 Months or Greater | | Total | |
|---|---|---|---|---|---|---|
| | Fair Value | Gross Unrealized Losses | Fair Value | Gross Unrealized Losses | Fair Value | Gross Unrealized Losses |
| U.S. Treasury securities | $ 16,392 | $ (1) | $ — | $ — | $ 16,392 | $ (1) |
| U.S. government agency obligations | 5,596 | (1) | — | — | 5,596 | (1) |
| Corporate bonds | 71,322 | (94) | — | — | 71,322 | (94) |
| Commercial paper | 39,445 | (23) | — | — | 39,445 | (23) |
| Total | $ 132,755 | $ (119) | $ — | $ — | $ 132,755 | $ (119) |

As of December 31, 2019 and 2018, the Company held a total of 16 out of 81 positions and 69 out of 84 positions, respectively, that were in an unrealized loss position, none of which had been in an unrealized loss position for 12 months or greater. Based on the Company's review of these securities, the Company believes that the cost basis of its available-for-sale marketable securities is recoverable and that, therefore, it had no other-than-temporary impairments on these securities as of December 31, 2019, or 2018. The Company does not intend to sell these debt securities before maturity and the Company believes it is not more likely than not that it will be required to sell these securities before the recovery of their amortized cost basis, which may be maturity.

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## 4. Accumulated Other Comprehensive Income (Loss)

The following table summarizes the changes in accumulated other comprehensive income (loss), or AOCI, net of tax, from unrealized gains (losses) on available-for-sale marketable securities, the Company's only component of AOCI, for the years ended December 31, 2019, 2018 and 2017.

| | Total Accumulated Other Comprehensive Income (Loss) |
|---|---|
| Balance, December 31, 2016 | $ 3 |
| Other comprehensive loss before reclassifications | (68) |
| Amount reclassified from accumulated other comprehensive income | (5) |
| Net current period other comprehensive loss | (73) |
| Balance, December 31, 2017 | (70) |
| Other comprehensive loss before reclassifications | (49) |
| Amount reclassified from accumulated other comprehensive loss | 5 |
| Net current period other comprehensive loss | (44) |
| Balance, December 31, 2018 | (114) |
| Other comprehensive income before reclassifications | 284 |
| Amount reclassified from accumulated other comprehensive loss | — |
| Net current period other comprehensive income | 284 |
| Balance, December 31, 2019 | $ 170 |

The reclassifications out of AOCI and into net loss were as follows:

| Component of AOCI | Year Ended December 31, 2019 | 2018 | 2017 | Affected Line Item in the Statements of Operations |
|---|---|---|---|---|
| Unrealized gains (losses) on available-for-sale marketable securities | | | | |
| Realized (losses) gains on sale of securities | $ — | $ (5) | $ 5 | Other income |
| | — | — | — | Benefit from income taxes |
| | $ — | $ (5) | $ 5 | |

The amounts reclassified out of AOCI into net loss were determined by specific identification.

## 5. Prepaid Expenses

As of December 31, 2019, the amount of prepaid expenses was $8,863, consisting of $8,498 of prepaid R&D clinical costs, $181 of prepaid insurance and $184 of other costs. As of December 31, 2018, the amount of prepaid expenses was $4,805, consisting of $4,377 of prepaid R&D clinical costs, $245 of prepaid insurance and $183 of other costs.

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## 6. Property and Equipment, Net

Property and equipment, net consists of the following:

| | December 31, | |
|---|---|---|
| | 2019 | 2018 |
| Computer and office equipment | $ 211 | $ 211 |
| Laboratory equipment | 628 | 628 |
| Furniture and fixtures | 61 | 47 |
| Leasehold improvements | 1,132 | 1,128 |
| | $ 2,032 | $ 2,014 |
| Less accumulated depreciation and amortization | 1,332 | 1,134 |
| Property and equipment, net | $ 700 | $ 880 |

Depreciation and amortization expense included in R&D expense and General and administrative expense was $198, $370 and $495 for the years ended December 31, 2019, 2018 and 2017, respectively.

During the year ended December 31, 2017, the Company wrote-off $7,816 of fully-depreciated Shelton property and equipment, including leasehold improvements, that was not re-located to the Stamford headquarters (see Note 17, *Commitments and Contingencies*). During the year ended December 31, 2017, the Company sold fully-depreciated Shelton property and equipment for net proceeds of $41.

## 7. Restricted Cash

The Company is required to maintain a stand-by letter of credit as a security deposit under its lease for its office space in Stamford, Connecticut (refer to Note 17, *Commitments and Contingencies: Leases*). The fair value of the letter of credit approximates its contract value. The Company's bank requires the Company to maintain a restricted cash balance to serve as collateral for the letter of credit issued to the landlord by the bank. As of December 31, 2019, the restricted cash balance for the Stamford lease was invested in a commercial money market account.

The letter of credit balance for the Stamford lease was required to remain at $769 through May 2019 and thereafter, upon request from the Company, was eligible to be reduced to $408 through the end of the lease term in November 2023. The reduction in the balance of the letter of credit for the Stamford lease was contingent upon the Company not being in default of any provisions of that lease prior to request for the reduction. In July 2019, the Company was granted the reduction in the balance of the letter of credit. As of December 31, 2019, the Company had $408 of restricted cash related to the Stamford lease in long-term assets. As of December 31, 2018, the Company had $361 of restricted cash related to the Stamford lease in current assets and $408 in long-term assets, respectively.

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported within the Balance Sheets that sum to the total of the same such amounts shown in the Statements of Cash Flows.

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Cash and cash equivalents | $ 18,305 | $ 15,081 |
| Restricted cash, current assets | — | 361 |
| Restricted cash, long-term assets | 408 | 408 |
| Total cash, cash equivalents, and restricted cash shown in the Statements of Cash Flows | $ 18,713 | $ 15,850 |

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## 8. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Accounts payable | $ 9,100 | $ 4,371 |
| Accrued research projects | 6,637 | 6,079 |
| Accrued professional fees | 635 | 802 |
| Accrued compensation and benefits | 3,293 | 2,370 |
| Total | $ 19,665 | $ 13,622 |

## 9. Stockholders' Equity

The Company's Board of Directors has authorized 100,000,000 shares of the Company's common stock, par value $0.001 per share, and 5,000,000 shares of undesignated preferred stock, par value $0.001 per share, that may be issued from time to time by the Board of Directors of the Company in one or more series. As of December 31, 2019, there were 46,720,225 shares of common stock and no shares of preferred stock issued and outstanding.

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are entitled to dividends when and if declared by the Board of Directors, subject to the preferential rights of the holders of preferred stock, if any.

In December 2019, as a result of the achievement of a clinical performance target, restricted stock units of various executive officers vested and were converted into 36,666 shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

On August 20, 2019, the Company entered into a Non-Exclusive License Agreement, or the Enteris License Agreement, with Enteris Biopharma, Inc., or Enteris (see Note 17, *Commitments and Contingencies* for additional information regarding the Enteris License Agreement). As consideration for the licensed rights under the Enteris License Agreement, the Company paid an upfront fee equal to $8,000, consisting of $4,000 in cash and $4,000 in shares of the Company's common stock. In connection with the Enteris License Agreement, on August 20, 2019, the Company entered into a Common Stock Purchase Agreement, or the Purchase Agreement, with Enteris and its affiliate, EBP Holdco LLC, collectively referred to as Purchaser, pursuant to which the Company issued and sold to Purchaser 170,793 shares of its common stock in a private placement in satisfaction of the $4,000 portion of the upfront fee payable in shares of the Company's common stock pursuant to the Enteris License Agreement, and for no additional consideration, based on a purchase price of $23.42 per share, which was equal to the 30-day volume weighted average price of the Company's common stock on August 20, 2019. In addition, if the Company exercises its right, but not obligation, to terminate its obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, it may elect to make 50% of the payment in stock by issuing additional shares of the Company's common stock valued at the 30-day volume weighted average price of the Company's common stock as of such exercise. Pursuant to its obligations under the Purchase Agreement, the Company effected the registration and sale of the shares issued and sold to Purchaser thereunder in accordance with the applicable requirements of the Securities Act of 1933, as amended, or the Securities Act, through the filing of an automatic shelf registration statement on Form S-3ASR (File No. 333-233666) with the SEC on September 9, 2019. In addition, the Purchase Agreement includes customary representations, warranties and covenants by the Company (see Note 17, *Commitments and Contingencies*).

On July 24, 2019, the Company entered into an underwriting agreement with J.P. Morgan Securities LLC and Jefferies LLC, as representatives of the several underwriters named therein, relating to the issuance and sale by the Company of 6,325,000 shares of its common stock, which included the exercise of the underwriters' option to purchase

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825,000 additional shares of common stock, at a public offering price of $23.00 per share. The Company closed this offering on July 29, 2019, including the full exercise of the underwriters' option to purchase 825,000 additional shares of common stock. The Company received net proceeds of $136,498, after deducting $8,977 of underwriting discounts and commissions and offering expenses.

This offering was made pursuant to the Company's Shelf Registration Statement on Form S-3 (File No. 333-230333), or the Shelf Registration Statement, filed with the SEC on March 15, 2019 and declared effective on April 4, 2019, and a related prospectus supplement dated July 24, 2019, which was filed with the SEC on July 25, 2019. The Shelf Registration Statement provides for aggregate offerings of up to $300,000 of common stock, preferred stock, debt securities, warrants or any combination thereof. The securities registered under the Shelf Registration Statement include unsold securities that had been registered under the Company's previous shelf registration statement (File No. 333-216657) that was declared effective on March 24, 2017.

In May 2019, as a result of the achievement of a clinical performance target, restricted stock units of various executive officers vested and were converted into 74,166 shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

On March 20, 2019, or the Effective Date, the Company entered into a consulting agreement with an existing stockholder. In accordance with the agreement, the stockholder provided various consulting services to the Company in exchange for 10,195 unregistered shares of the Company's common stock. The closing price of the Company's common stock on the Effective Date was $19.37 per share. The services provided by the consultant were performed during the six-month period following the Effective Date. During the year ended December 31, 2019, stock-based compensation expense of $197 was recognized in the Statements of Comprehensive Loss, all of which related to G&A expense.

In December 2018, as a result of the achievement of a clinical performance target, restricted stock units of various executive officers vested and were converted into 83,791 shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

On July 18, 2018, the Company entered into an underwriting agreement with Jefferies LLC and Merrill Lynch, Pierce, Fenner & Smith Incorporated, as representatives of the several underwriters named therein, relating to the issuance and sale by the Company of up to 5,175,000 shares of its common stock, including 675,000 shares of common stock the underwriters had the option to purchase, at a public offering price of $19.00 per share. This offering was made pursuant to the Company's Registration Statement on Form S-3 (File No. 333-216657), filed with the SEC on March 13, 2017 and declared effective on March 24, 2017, and a related prospectus dated March 24, 2017 and prospectus supplement dated July 18, 2018, which was filed with the SEC on July 20, 2018.

On July 23, 2018, the Company closed the offering, including the full exercise of the underwriters' option to purchase 675,000 additional shares of common stock. The Company received net proceeds of $92,063, after deducting $6,262 relating to underwriting discounts and commissions and offering expenses.

On May 17, 2018, the Company issued 1,174,827 shares of its common stock to Vifor in connection with the license agreement entered into with VFMCRP (refer to Note 11, *Collaboration and Licensing Agreements*).

On March 30, 2017, the Company entered into an underwriting agreement with Piper Jaffray & Co. and Stifel, Nicolaus & Company, Incorporated, as representatives of the several underwriters named therein, relating to the issuance and sale by the Company of 5,117,500 shares of its common stock, including 667,500 shares of common stock the underwriters had the option to purchase, at a public offering price of $18.00 per share, or the 2017 Offering. The 2017 Offering was made pursuant to the Company's Registration Statement on Form S-3 (File No. 333-216657), filed with the

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SEC on March 13, 2017 and declared effective on March 24, 2017, and a related prospectus supplement dated March 30, 2017, which was filed with the SEC on March 31, 2017.

On April 5, 2017, the Company closed the 2017 Offering, including the full exercise of the underwriters' option to purchase 667,500 additional shares of common stock. The Company received net proceeds of $86,224, after deducting $5,891 relating to underwriting discounts and commissions and offering expenses.

**10. Fair Value Measurements**

The following tables summarize the Company's financial assets measured at fair value on a recurring basis as of December 31, 2019 and 2018 and by level within the fair value hierarchy:

Fair value measurement as of December 31, 2019:

| Financial assets<br>Type of Instrument | Total | Quoted prices in active markets for identical assets (Level 1) | Significant other observable inputs (Level 2) | Significant unobservable inputs (Level 3) |
|---|---|---|---|---|
| **Cash and cash equivalents:** | | | | |
| Money market funds and checking accounts | $ 18,305 | $ 18,305 | $ — | $ — |
| **Available-for-sale marketable securities:** | | | | |
| U.S. Treasury securities | 16,081 | — | 16,081 | — |
| U.S. government agency obligations | 25,816 | — | 25,816 | — |
| Corporate bonds | 115,890 | — | 115,890 | — |
| Commercial paper | 38,573 | — | 38,573 | — |
| Municipal bonds | 3,500 | — | 3,500 | — |
| **Restricted cash:** | | | | |
| Commercial money market account | 408 | 408 | — | — |
| Total financial assets | $ 218,573 | $ 18,713 | $ 199,860 | $ — |

Fair value measurement as of December 31, 2018:

| Financial assets<br>Type of Instrument | Total | Quoted prices in active markets for identical assets (Level 1) | Significant other observable inputs (Level 2) | Significant unobservable inputs (Level 3) |
|---|---|---|---|---|
| **Cash and cash equivalents:** | | | | |
| Money market funds and checking accounts | $ 15,081 | $ 15,081 | $ — | $ — |
| **Available-for-sale marketable securities:** | | | | |
| U.S. Treasury securities | 19,539 | — | 19,539 | — |
| U.S. government agency obligations | 17,859 | — | 17,859 | — |
| Corporate bonds | 75,910 | — | 75,910 | — |
| Commercial paper | 50,390 | — | 50,390 | — |
| Municipal bonds | 4,000 | — | 4,000 | — |
| **Restricted cash:** | | | | |
| Commercial money market account | 769 | 769 | — | — |
| Total financial assets | $ 183,548 | $ 15,850 | $ 167,698 | $ — |

There were no purchases, sales or maturities of Level 3 financial assets and no unrealized gains or losses related to Level 3 available-for-sale marketable securities for the years ended December 31, 2019, 2018 and 2017. There were no

transfers of financial assets between Levels 1, 2, or 3 classifications during the years ended December 31, 2019 and 2018.

**11. Collaboration and Licensing Agreements**

*Vifor Fresenius Medical Care Renal Pharma Ltd.*

On May 17, 2018, the Company entered into a license agreement, or the VFMCRP Agreement, with VFMCRP under which the Company granted VFMCRP an exclusive, royalty-bearing license, or the VFMCRP License, to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize CR845/difelikefalin injection, or the Licensed Product, for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients, or the Field, worldwide (excluding the United States, Japan and South Korea), or the Territory. VFMCRP cannot perform development activities on their own unless specifically allocated to VFMCRP by the Joint Development Committee, or JDC, and Joint Steering Committee, or JSC. The Company's membership on the JSC or JDC is at its sole discretion and is not its obligation.

The Company is responsible, at its own cost, to undertake clinical and non-clinical development, or the R&D services. The Company is also responsible to provide all content and subject matter expertise required for registration with the European Medicines Agency, or EMA, in the European Union, or the EU, that will be needed by VFMCRP for such registration, including participation in regulatory meetings, as needed. If third-party costs incurred by the Company with respect to its clinical development for the EMA registration exceed $20,000, such excess costs will be shared equally by the Company and VFMCRP. VFMCRP will contribute, at its own cost, its clinical development expertise as reasonably useful for such development activities, such as preparing the clinical results that the Company presents to it in a format acceptable to the EMA to obtain marketing approval in the EU.

The Company has identified two performance obligations under ASC 606: (1) granting of the VFMCRP License and (2) the R&D services. The Company has determined that these two performance obligations are not capable of being distinct (i.e., do not have standalone value for VFMCRP) because VFMCRP cannot benefit (derive potential cash flows) from either one on its own or together with other resources that are readily available to it since VFMCRP is relying on the Company's expertise in investigating chronic kidney disease-associated pruritus, or CKD-aP, and its know-how obtained from multiple years of pre-clinical and clinical development, and years of interactions with the FDA which other companies or CROs would not have. The VFMCRP License does not provide benefit to VFMCRP until and unless the Company conducts the pivotal clinical trials and other supportive trials in CKD-aP to gather sufficient clinical data for VFMCRP to obtain marketing approval in the Territory. Furthermore, VFMCRP does not have the right to perform development activities on its own unless specifically allocated by the JDC or JSC.

The two identified performance obligations are also not distinct within the context of the contract, (i.e., are not separately identifiable from each other) because of the nature of the promise within the context of the contract. The nature of the promise is to transfer a combined deliverable to VFMCRP based on the agreement (to support the ability of VFMCRP to commercialize the Licensed Product) and the Company determined that the VFMCRP License and the R&D services are inputs rather than a transfer of each of these goods and services individually. In addition, the two identified performance obligations are highly interrelated and interdependent because satisfaction of both performance obligations is required for VFMCRP to derive benefit from the VFMCRP Agreement for commercialization of the Licensed Product in the Territory. Therefore, the two performance obligations are not distinct from each other and are accounted for as a single performance obligation.

Upon entry into the VFMCRP Agreement, VFMCRP made a non-refundable, non-creditable $50,000 upfront payment to the Company and Vifor purchased 1,174,827 shares of the Company's common stock, or the Vifor Shares, for $20,000 at a price of $17.024 per share, which represents a premium over a pre-determined average closing price of

the Company's common stock. The purchase of the Company's common stock was governed by a separate stock purchase agreement. The excess of the stock purchase price over the cost of the Vifor Shares at the closing price of the Company's common stock on the purchase date of $5,444 was added to the upfront payment for accounting purposes.

The Company is eligible to receive from VFMCRP regulatory and commercial milestone payments in the aggregate of up to $470,000, consisting of up to $30,000 in regulatory milestones and up to $440,000 in tiered commercial milestones, all of which are sales-related. The Company is also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined in the VFMCRP Agreement, of CR845/difelikefalin injection in the Licensed Territories. The Company retains full commercialization rights for CR845/difelikefalin injection for the treatment of CKD-aP in the United States except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where VFMCRP and the Company will promote CR845/difelikefalin injection under a profit-sharing arrangement (subject to the terms and conditions of the VFMCRP Agreement) based on net FMCNA clinic sales recorded by the Company.

At inception of the VFMCRP Agreement, there was significant uncertainty as to whether marketing approval would be obtained in the Territory for the Licensed Product. Therefore, at that time, there was a significant probability that any potential revenue from sales of the Licensed Product that would be included in the transaction price would be reversed when the uncertainty is resolved. Consequently, any sales royalties and sales milestones are constrained from the transaction price at inception of the VFMCRP Agreement and will be recognized as revenue if, and when, such sales transactions occur in the future.

At inception of the VFMCRP Agreement, the transaction price of $55,444 was allocated entirely to the one combined performance obligation, as described above, and was initially recorded as deferred revenue. License and milestone revenue will be recognized proportionately as the R&D services are conducted (i.e., prior to submission of an NDA).

The license also requires VFMCRP to promote and take orders in the U.S. for sale by the Company to FMC U.S. Dialysis Clinics and allows VFMCRP to grant sub-licenses, which, in certain cases, requires the Company's prior written consent. The Company retains the rights to import, distribute, promote, sell and otherwise commercialize the Licensed Product outside of the Field and outside of the Territory.

The Company retains the rights to make and have made the Licensed Product in the Territory for commercial sale by VFMCRP in the Field in or outside the Territory and for supply of Licensed Product to VFMCRP under the terms of a supply agreement, or the Supply Agreement. The supply price will be the Company's cost of goods sold, as calculated under U.S. GAAP, plus an agreed upon margin. The Supply Agreement will co-terminate with the VFMCRP Agreement. In regards to a supply agreement, the VFMCRP Agreement only includes a requirement for the Company to negotiate in good faith with VFMCRP. After the execution of the VFMCRP Agreement, a separate agreement to supply them with the Licensed Product would be entered into, although the Company has no obligation to execute a supply agreement. In the event that the parties fail to enter into a Supply Agreement or if the Company fails to provide Licensed Product on a timely basis, VFMCRP has the right to manufacture or have manufactured the Licensed Product in and outside the Territory.

The Supply Agreement will be accounted for as a customer option that is not a material right because the selling price of the Licensed Product under the Supply Agreement is the Company's cost of goods sold plus an agreed upon margin, which is commensurate with the "cost of goods sold plus" model that the Company would charge other parties under similar agreements (the standalone selling price) and not at a discount. Therefore, the sale of clinical compound to VFMCRP is not a performance obligation under the VFMCRP Agreement but rather the Supply Agreement is a separate agreement from the VFMCRP Agreement. The only performance obligation under the Supply Agreement is the delivery of the Licensed Product to VFMCRP for commercialization. Revenue from the sale of the Licensed Product to

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VFMCRP will be recognized as Clinical Supply revenue in the Company's Statements of Comprehensive Loss as sales of the Licensed Product occur. As of December 31, 2019, no supply agreement has been entered into between the Company and VFMCRP.

The VFMCRP Agreement terminates upon the expiration of all royalty terms with respect to the Licensed Products, which expire on a Product-by-Product and country-by-country basis, at the latest of (a) the expiration of all patent rights licensed to VFMCRP covering such Licensed Product; (b) the expiration of all regulatory and data exclusivity applicable to such Licensed Product in such country and (c) the tenth anniversary of the first commercial sale of such Product in such country.

The VFMCRP Agreement may be terminated earlier by either party for material breach that is not cured within 60 days, bankruptcy by either party and by both parties upon mutual written consent. The Company may terminate the VFMCRP Agreement if VFMCRP challenges the validity of any licensed patent rights, except if such patent challenge results from the Company's action against VFMCRP for infringement of any licensed patent in the Territory. In addition, upon the earlier of (1) the acceptance for filing of an NDA covering Licensed Product filed with the FDA (after completion of the Phase 3 program) or (2) the third anniversary of the Effective Date, the VFMCRP Agreement may be terminated by VFMCRP in its entirety or with respect to any countries within the Territory upon written notice to the Company. Such termination will be effective twelve months following the date of such notice.

If the VFMCRP Agreement terminates early for any reason stated above, VFMCRP's licenses will terminate, VFMCRP's rights to use the Company's confidential information and the Company's know-how will revert to the Company and VFMCRP will assign and transfer to the Company all right, title and interest in all regulatory applications (IND's and NDA's), regulatory approval applications and regulatory approvals in the Territory covering Licensed Product.

*Maruishi Pharmaceutical Co., Ltd.*

In April 2013, the Company entered into a license agreement with Maruishi, or the Maruishi Agreement, under which the Company granted Maruishi an exclusive license to develop, manufacture, and commercialize drug products containing CR845/difelikefalin for acute pain and/or uremic pruritus in Japan. Maruishi has the right to grant sub-licenses in Japan, which entitles the Company to receive sub-license fees, net of prior payments made by Maruishi to the Company. Under the Maruishi Agreement, the Company and Maruishi are required to use commercially reasonable efforts, at their own expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States and Japan, respectively. In addition, the Company provided Maruishi specific clinical development services for CR845/difelikefalin used in Maruishi's field of use.

Under the Maruishi Agreement, the Company identified two performance obligations in accordance with ASC 606: (1) the license; and (2) the R&D services specific to the uremic pruritus field of use (specified as Phase 1 and proof-of-concept clinical trials), both of which were determined to have standalone value. The Company determined that these performance obligations had standalone value due to the fact that Maruishi obtained the right to develop the compound on its own and the Company was specifically contracted to perform specific R&D services as noted above. The Company believes that these early stage R&D services performed by the Company did not require any specific expertise or know-how, but rather could have been completed by outside third parties, therefore providing standalone value to Maruishi.

In March 2017, Maruishi entered into a sub-license agreement with Kissei Pharmaceutical Co. Ltd., or Kissei, for the development and sales/marketing of CR845/difelikefalin (called MR13A9 by Maruishi) for the treatment of uremic pruritus in dialysis patients in Japan. Consequently, for the year ended December 31, 2017, the Company recognized revenue of $843 related to the sub-license fee. The Company allocated the amount of the sub-license fee to each of the

two identified performance obligations in the same proportion as the upfront license fee that the Company received at inception of the Maruishi Agreement. Accordingly, $530 was recognized as license and milestone fees revenue and $313 was recognized as collaborative revenue.

Under the terms of the Maruishi Agreement, the Company is eligible to receive milestone payments upon the achievement of defined clinical and regulatory events as well as tiered, low double-digit royalties with respect to any sales of the licensed product sold in Japan by Maruishi, if any, and share in any sub-license fees.

During the years ended December 31, 2019, 2018 and 2017, the Company recognized clinical compound revenue of $140, $33 and $68, respectively, from the sale of clinical compound to Maruishi.

The Company incurred R&D expense related to the Maruishi Agreement of $126, $30 and $61 (all related to the cost of clinical compound sold to Maruishi) during the years ended December 31, 2019, 2018 and 2017, respectively.

*Chong Kun Dang Pharmaceutical Corporation*

In April 2012, the Company entered into a license agreement, or the CKDP Agreement, with Chong Kun Dang Pharmaceutical Corporation, or CKDP, in South Korea, under which the Company granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in South Korea. The Company and CKDP are each required to use commercially reasonable efforts, at their respective expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States and South Korea, respectively. The Company identified the granting of the license as its only performance obligation under the CKDP Agreement.

Under the terms of the CKDP Agreement, the Company is eligible to receive milestone payments upon the achievement of defined clinical and regulatory events as well as tiered royalties, with percentages ranging from the high single digits to the high teens, based on net sales of products containing CR845/difelikefalin in South Korea, if any, and share in any sub-license fees.

**12. Revenue Recognition**

The Company currently recognizes revenue in accordance with ASC 606, as amended, for the VFMCRP, Maruishi and CKDP agreements (see Note 11, *Collaboration and Licensing Agreements*). Under each of these agreements, the Company has recognized revenue from upfront payments and, under the Maruishi Agreement and the CKDP Agreement, from clinical development milestone payments. The Company has also recognized revenue from a sub-license payment earned under the Maruishi Agreement. Under the Maruishi Agreement and the CKDP Agreement, the Company may earn additional future milestone payments upon the achievement of defined clinical events, and under the VFMCRP Agreement, the Maruishi Agreement and the CKDP Agreement upon the achievement of defined regulatory events and, under the VFMCRP Agreement and the Maruishi Agreement, from sales milestones. The Company may also recognize revenue in the future from royalties on net sales under all three agreements. In addition, the Company has recognized revenue upon the delivery of clinical compound to Maruishi in accordance with separate supply agreements.

*Contract balances*

As of December 31, 2019, the Company had deferred revenue, current of $22,262 related to the performance obligations from the VFMCRP Agreement and had no balances of receivables, other assets or deferred revenue, non-current related to the VFMCRP Agreement. There were no balances of receivables, other assets or deferred revenue relating to the Maruishi and CKDP agreements as of December 31, 2019. As of December 31, 2018, the Company had deferred revenue, current of $26,825 and deferred revenue, non-current of $15,184 related to the performance obligations from the VFMCRP Agreement and had no balances of receivables or other assets related to the VFMCRP

Agreement. There were no balances of receivables, other assets or deferred revenue relating to the Maruishi and CKDP agreements as of December 31, 2018.

*Performance obligations*

Under the VFMCRP Agreement, the Company's performance obligations of granting a license to allow VFMCRP to commercialize CR845/difelikefalin injection worldwide, except in the United States, Japan and South Korea, which occurred at inception of the contract in May 2018, and performing R&D services by the Company to obtain sufficient clinical data which will be shared with VFMCRP to allow them to receive regulatory approval to sell CR845/difelikefalin in the licensed territory, are not distinct, and are accounted for as a single performance obligation during the period that the R&D services are rendered (see Note 11, *Collaboration and Licensing Agreements*).

The Company's distinct performance obligations under the Maruishi Agreement include transfer of the license to the Company's IP, which allowed Maruishi to develop and commercialize CR845/difelikefalin, for acute pain and uremic pruritus indications in Japan, which occurred at inception of the contract in 2013, and performance of R&D services, which occurred from 2013 to 2015, as those services were rendered. The Company agreed to conduct limited work on an oral tablet formulation of CR845/difelikefalin and to conduct Phase 1 and proof-of-concept Phase 2 clinical trials of an intravenous formulation of CR845/difelikefalin to be used to treat patients with uremic pruritus. The Company agreed to transfer the data and information from such development to Maruishi for its efforts to obtain regulatory approval in Japan. These activities are referred to as R&D services.

The Company's only performance obligation under the supply agreement with Maruishi is to deliver clinical compound to Maruishi in accordance with the receipt of purchase orders. If and when the Company enters into a supply agreement with VFMCRP, the Company's only performance obligation under this supply agreement would be to deliver CR845/difelikefalin injection to VFMCRP in accordance with the receipt of purchase orders.

Under the CKDP Agreement, the Company's only performance obligation is to transfer the license to the Company's IP related to CR845/difelikefalin, which occurred at inception of the contract in 2012.

Upon execution of the VFMCRP Agreement, the Maruishi Agreement and the CKDP Agreement, the Company received a single fixed payment from each counterparty in exchange for granting the respective licenses and performing its other obligations. In addition, each of the counterparties made an equity investment in the Company's common stock.

*Transaction price allocated to the remaining performance obligations*

At inception of the VFMCRP Agreement, the entire transaction price of $55,444 was allocated to the one combined performance obligation, as described above. As of December 31, 2019, $33,182 of that amount was recognized as license and milestone fees revenue based on the percentage of R&D services that had been completed. As of December 31, 2019, there were no remaining performance obligations under either the Maruishi Agreement or the CKDP Agreement, although the Company is eligible to receive milestone payments and sales royalties in the future.

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*Significant judgments*

In applying ASC 606, as amended, to its three contracts, the Company made the following judgments that significantly affect the timing and amount of revenue recognition:

1. *Determination of the number of distinct performance obligations in a contract*

The VFMCRP Agreement contains one combined performance obligation, which includes the Company's two performance obligations to grant a license to VFMCRP and conduct R&D services. Both of those performance obligations are inputs to the promise, within the context of the contract, to transfer a combined output for which VFMCRP has contracted (the ability of VFMCRP to commercialize the Licensed Product) (see Note 11, *Collaboration and Licensing Agreements*, for further discussion).

The Maruishi Agreement contains two distinct performance obligations: the granting of the license and the promise to deliver defined R&D services. Under the Maruishi Agreement, the license and the R&D services represent distinct goods or services from each other because Maruishi is able to benefit from the license on its own or together with other resources that are readily available to it (i.e., capable of being distinct). Maruishi's ability to benefit from the license without the R&D services is indicated by its ability to conduct clinical trials of CR845/difelikefalin on its own and by the provision in the Maruishi Agreement whereby if the Company suspends or discontinues its development activity, the Company will provide information regarding its development efforts up to that point so that Maruishi may continue development and commercialization of the product in Japan. Therefore, the R&D services do not significantly affect Maruishi's ability to use and benefit from the license.

In addition, the Company's promise in the Maruishi contract to transfer the license is separately identifiable from the promise to provide defined R&D services (i.e., distinct within the context of the contract) because the Company is not using the goods or services as inputs to produce or deliver the combined output or outputs specified by the customer. The combined output specified by Maruishi is its right to conduct development activities related to CR845/difelikefalin in Japan, which could result in regulatory approval in Japan. That right is derived from the Company's grant of the license. Maruishi is conducting clinical trials on its own and does not require the R&D services provided by the Company. Furthermore, the R&D services do not significantly modify or customize the license and vice versa. Finally, the license and R&D services are not highly interdependent or highly interrelated because the Company is able to fulfill its promise to transfer the initial license independently from its promise to subsequently provide the R&D services, which Maruishi can obtain on its own.

The only performance obligation in the CKDP Agreement is the granting of the license.

2. *Determination of the transaction price, including whether any variable consideration is included at inception of the contract*

The transaction price is the amount of consideration that the Company expects to be entitled to in exchange for transferring promised goods or services to the customer. The transaction price must be determined at inception of a contract and may include amounts of variable consideration. However, there is a constraint on inclusion of variable consideration, such as milestone payments or sales-based royalty payments, in the transaction price related to licenses of IP, if there is uncertainty at inception of the contract as to whether such consideration will be recognized in the future (see Note 2, *Significant Accounting Policies: Revenue Recognition*).

The decision as to whether or not it is probable that a significant reversal of revenue will occur in the future, depends on the likelihood and magnitude of the reversal and is highly susceptible to factors outside the entity's influence (for example, the Company cannot determine the outcome of clinical trials; the Company cannot determine if or when

they or the counterparty will initiate or complete clinical trials; and the Company's ability to obtain regulatory approval is difficult). In addition, the uncertainty is not expected to be resolved for a long period of time (in the order of years) and finally, the Company has limited experience in the field.

Therefore, at inception of the VFMCRP Agreement, the Maruishi Agreement and the CKDP Agreement, milestones and sales-based royalty payments were not included in the transaction price based on the factors noted above.

Under the VFMCRP Agreement, the single combined performance obligation will be satisfied as the R&D services are rendered and the transaction price, including the upfront payment of $50,000 and the premium on the common stock purchased by VFMCRP of $5,444, will be recognized as revenue as the R&D services are performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation. The remaining potential consideration was considered to be variable consideration and was constrained at inception of the contract, including regulatory and sales milestones and sales royalties (see Note 11, *Collaboration and Licensing Agreements*).

All performance obligations under the Maruishi Agreement and the CKDP Agreement were satisfied by the end of 2015. In the future, any milestone event will be recognized in accordance with Note 2, *Significant Accounting Polices: Revenue Recognition*, as milestone and license fee revenue and collaboration revenue based upon the relative standalone selling prices of the two performance obligations at inception of the Maruishi Agreement, and as milestone and license fee revenue under the CKDP Agreement.

Under the Maruishi Agreement, the transaction price includes only the non-refundable and non-creditable upfront license fee of $15,337, including the premium of $337 from the sale of Company stock to Maruishi, that was paid to the Company at inception of the contract. The remaining potential consideration was considered to be variable consideration and was constrained at inception of the contract, including an aggregate of up to $10,500, which the Company is eligible to receive upon achievement of clinical development and regulatory milestones, a one-time sales milestone of one billion Yen when a certain sales level is attained; a mid-double-digit percentage of all non-royalty payments received by Maruishi from its sub-licensees, if any; and tiered royalties based on net sales of products containing CR845/difelikefalin in Japan, if any, with minimum royalty rates in the low double digits and maximum royalty rates in the low twenties.

Under the CKDP Agreement, the transaction price includes only the non-refundable and non-creditable upfront license fee of $646, including the premium of $83 from the sale of Company stock to CKDP, that was paid to the Company at inception of the contract. The remaining consideration was considered to be variable consideration and was constrained at inception of the contract, including an aggregate of up to $3,750, which the Company is eligible to earn upon achievement of clinical development and regulatory milestones. The Company is also eligible to receive a mid-double-digit percentage of all non-royalty payments received by CKDP from its sub-licensees, if any, and tiered royalties ranging from the high single digits to the high teens based on net sales of products containing CR845/difelikefalin in South Korea, if any.

*3. Determination of the estimate of the standalone selling price of performance obligations*

In order to recognize revenue under ASC 606, as amended, for contracts for which more than one distinct performance obligation has been identified, the Company must allocate the transaction price to the performance obligations based upon their standalone selling prices. The best evidence of standalone selling price is an observable price of a good or service when sold separately by an entity in similar circumstances to similar customers. If such evidence is not available, standalone selling price should be estimated so that the amount that is allocated to each performance obligation equals the amount that the entity expects to receive for transferring goods or services. The Company has identified more than one performance obligation only in the Maruishi Agreement. Since evidence based on observable prices is not available for the performance obligations under the Maruishi Agreement, the Company

considered market conditions and entity-specific factors, including those contemplated in negotiating the agreements, as well as certain internally developed estimates.

At inception of the Maruishi Agreement, the Company determined the estimate of standalone selling price for the license performance obligation by using the adjusted market assessment approach. Under this method, the Company forecasted and analyzed CR845/difelikefalin in the Japanese market, the phase of clinical development as well as considered recent similar license arrangements within the same phase of clinical development, therapeutic area, type of agreement, etc. To estimate the standalone selling price of the R&D services, the Company forecasted its expected costs of satisfying that performance obligation and added a margin for that service.

*4. Determination of the method of allocation of the transaction price to the distinct performance obligations*

At inception of the Maruishi Agreement, the Company allocated the transaction price of $15,337 between the two performance obligations based on their relative standalone selling prices, determined as described above. The Company determined that the license and the R&D services had estimated standalone selling prices of $10,200 and $6,200, respectively. The resulting percentage allocations were applied to the $15,337 of total transaction price, which resulted in $9,637 being allocated to the license performance obligation, which was recognized immediately as license revenue, while $5,700 was allocated to the R&D services performance obligation. The amount allocated to the R&D services performance obligation was initially recorded as deferred revenue and was recognized as collaborative revenue as the R&D services were provided through July 2015.

Since both the VFMCRP Agreement and the CKDP Agreement each contain only one distinct performance obligation, at the inception of each of those agreements, the entire transaction price was allocated to the respective performance obligation.

*5. Determination of the timing of revenue recognition for contracts*

Revenue should be recognized when, or as, an entity satisfies a performance obligation by transferring a promised good or service to a customer; i.e., when the customer obtains control of the good or service. The licenses granted to both Maruishi and CKDP are being accounted for as distinct performance obligations. As discussed below, both licenses relate to functional IP for which revenue is recognized at a point in time – in the case of these two license agreements, the point in time is at inception of the contract because the customer obtained control of the license at that point.

The licenses grant Maruishi and CKDP the right to use the Company’s IP relating to CR845/difelikefalin as it existed at the point in time that the licenses were granted. That IP has significant standalone functionality as it provides the customer with the ability to perform a function or task, such as to manufacture CR845/difelikefalin and conduct clinical trials, and is considered to be functional IP.

During the license periods, the Company is continuing to develop and advance CR845/difelikefalin by conducting clinical trials. Those development efforts are for its own benefit and do not substantively change the significant standalone functionality of the licensed IP granted to Maruishi or CKDP. Therefore, the Company’s ongoing development efforts do not significantly affect the IP’s utility to which Maruishi or CKDP have rights. Furthermore, if the Company abandons its development efforts, Maruishi or CKDP may still continue to develop CR845/difelikefalin in their respective countries.

The R&D services performance obligation under the Maruishi Agreement represents a separate performance obligation. The R&D services were provided to Maruishi by the Company from inception of the agreement in 2013 through the third quarter of 2015, at which time the Company had fulfilled its promise related to the R&D services.

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Revenue related to the R&D services performance obligation was recognized as services were performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation.

Similarly, under the VFMCRP Agreement, revenue related to the single distinct performance obligation, which includes both granting of the license and performance of the R&D services, will be recognized as the R&D services are performed, based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation. The Company expects that the remaining amount of the transaction price that was allocated to the combined performance obligation of $22,262 at December 31, 2019 will be recognized by 2020, as the R&D services are performed, subject to certain development and regulatory uncertainties.

6. *Determination of consideration as variable consideration, including factors related to inclusion in the transaction price at inception of the contract and timing of recognition as revenue.*

The VFMCRP Agreement, the Maruishi Agreement and the CKDP Agreement contain potential payments related to achievement of defined milestone events and royalties upon net sales of future products, which are considered to be variable consideration because of the uncertainty of occurrence of any of those events specified in those agreements at inception of the agreements. Therefore, those potential payments were not included in the transaction price at the inception of the agreements.

Revenue related to achievement of milestone events is recognized when the Company has determined that it is probable that a milestone event will be achieved and there will not be a significant reversal of revenue in future periods. Upon probability of achievement of a milestone event, the most likely amount of variable consideration is included in the transaction price. Subsequent changes to the transaction price, after contract initiation, are allocated to the performance obligations in the contract on the same basis as at contract inception. Revenue for variable consideration is recognized in the same manner (point in time or over time) as for the performance obligations to which the payment amounts were allocated.

The Maruishi Agreement and the CKDP Agreement specify that certain development milestones will be achieved at pre-specified defined phases of a clinical trial (such as initiation or completion or other pre-specified time during a clinical trial as specified in the agreements).

During the years ended December 31, 2019, 2018 and 2017, no milestone events were probable of occurrence or achieved.

*Sublicense payments*

VFMCRP’s, Maruishi’s and CKDP’s right to grant sub-licenses is explicitly stated in their respective license agreements. The amount of any potential sub-license fees to be received by the Company, which is based on a formula, is considered to be variable consideration and is constrained from inclusion in the transaction price at inception of the contract since at that time it was probable that there would be a reversal of such revenue in the future because the Company did not know if a sublicense would be granted in the future.

In March 2017, Maruishi entered into a sub-license agreement to the Maruishi Agreement with Kissei in Japan for development and sales/marketing of CR845/difelikefalin for the treatment of uremic pruritus in dialysis patients in Japan. The Company first learned that the terms of the sub-license agreement had been finalized less than a month before the sub-licensee publicly announced the agreement. At that time, the Company determined that the sub-license fee would not be constrained from inclusion in the transaction price. Consequently, the Company included the amount of the sub-license fee in the transaction price and recognized revenue of $843 in the same manner as described above for milestone payments.

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*Sales-based Royalty Payments*

The VFMCRP Agreement, CKDP Agreement and Maruishi Agreement each allow the Company to earn sales-based royalty payments in exchange for a license of intellectual property. In that case, the Company will recognize revenue for a sales-based royalty only when (or as) the later of the following events occurs:

a. The subsequent sale or usage occurs.

b. The performance obligation to which some or all of the sales-based royalty has been allocated has been satisfied (or partially satisfied).

Since the sale (item a, above) occurs after the license was delivered (item b, above), the sales-based royalty exception, to exclude such royalty payments from the transaction price, applies to the overall revenue stream. Therefore, sales-based royalty payments are recognized as revenue when the customer's sales occur. To date, no royalties have been earned or were otherwise due to the Company.

**13. Stock-Based Compensation**

***2019 Inducement Plan***

On October 30, 2019, the Company's Board of Directors adopted the 2019 Inducement Plan, or the 2019 Plan, which is a non-stockholder approved stock plan adopted pursuant to the "inducement exception" provided under Nasdaq Listing Rule 5635(c)(4), or Rule 5635, for the purpose of awarding (i) non-statutory stock options, (ii) restricted stock awards, (iii) restricted stock unit awards, (iv) other stock awards (collectively, the Inducement Awards) to new employees of the Company, as inducement material to such new employees entering into employment with the Company. On November 20, 2019, the Company filed a Registration Statement on Form S-8 with the SEC covering the offering of up to 300,000 shares of its common stock, par value $0.001, pursuant to the Company's 2019 Plan. During the year ended December 31, 2019, the Company granted 47,500 stock options under the 2019 Plan to new employees. Initial grants of Inducement Awards made to employees vest as to 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months and subsequent grants vest monthly over a period of four years from the grant date.

***2014 Equity Incentive Plan***

The Company's 2014 Equity Incentive Plan, or the 2014 Plan, is administered by the Company's Board of Directors or a duly authorized committee thereof, referred to as the Plan administrator. The 2014 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights, performance stock awards and other forms of equity compensation, collectively referred to as Stock Awards. Additionally, the 2014 Plan provides for the grant of performance cash awards. Incentive stock options may be granted only to employees. All other awards may be granted to employees, including officers, non-employee directors, and consultants. No incentive stock options may be granted under the 2014 Plan after the tenth anniversary of the effective date of the 2014 Plan. Stock Awards granted under the 2014 Plan vest at the rate specified by the Plan administrator. Initial grants of Stock Awards made to employees and non-employee consultants generally vest as to 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months and subsequent grants vest monthly over a period of four years from the grant date. Beginning in 2018, stock options initially granted to members of the Company's Board of Directors vest over a period of three years in equal installments from the date of the grant, subject to the option holder's continued service as a Director through such date. Subsequent grants to Directors that are made automatically at Annual Meetings of Stockholders vest fully on the first anniversary of the date of grant. The Plan administrator determines the term of Stock Awards granted under the 2014 Plan up to a maximum of ten years.

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The aggregate number of shares of the Company's common stock reserved for issuance under the 2014 Plan has automatically increased on January 1 of each year, beginning on January 1, 2015 and will continue to increase on January 1 of each year through and including January 1, 2024, by 3% of the total number of shares of the Company's capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by the Company's Board of Directors. On January 1, 2020, the aggregate number of shares of common stock that may be issued pursuant to Stock Awards under the 2014 Plan automatically increased from 6,086,907 to 7,488,513. The maximum number of shares that may be issued pursuant to the exercise of incentive stock options under the 2014 Plan is 30,000,000 shares.

*Restricted Stock Units*

In June 2019, the Board of Directors, upon the recommendation of the Compensation Committee, amended the Company's non-employee director compensation policy. Pursuant to the terms of the amended policy, each non-employee director was entitled to receive, at the time of the Company's 2019 Annual Meeting of Stockholders, 6,000 restricted stock units. As a result, on June 4, 2019, the date of the Company's 2019 Annual Meeting of Stockholders, an aggregate of 24,000 restricted stock units were granted to Directors under the 2014 Plan with a grant date fair value of $20.47 per share. The restricted stock units vest on the earlier of (i) June 4, 2020 and (ii) immediately prior to the Company's next Annual Meeting of Stockholders following the grant date, subject to the recipient's continued service through such date. As a result, the Company will recognize compensation expense associated with these restricted stock units ratably over the one-year vesting period following the grant date. For the year ended December 31, 2019, $287 of stock compensation expense relating to the Board of Directors' restricted stock units was recognized in the Statements of Comprehensive Loss, all of which related to G&A expense. None of the 24,000 restricted stock units vested or were settled in shares of the Company's common stock as of December 31, 2019.

In March 2019, the Compensation Committee of the Company's Board of Directors approved and granted a total of 215,000 restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $16.10 per share. Vesting of the restricted stock units was contingent on the achievement of certain performance targets, subject to the recipient's continuous service through the vesting events. At the date of grant, the Company concluded that the probability of achievement of the performance targets could not be determined until they were achieved, and accordingly, the Company would recognize compensation expense associated with these awards when, and to the extent, the restricted stock units vested in accordance with achievement of the performance targets. In December 2019 and May 2019, performance targets relating to 36,666 and 74,166 restricted stock units, respectively, had been achieved and thus such restricted stock units vested and the awards were settled in shares of common stock. As a result, $1,784 of stock compensation expense relating to the vesting of these restricted stock units was recognized in the Statements of Comprehensive Loss for the year ended December 31, 2019, consisting of $1,180 relating to G&A expense and $604 relating to R&D expense.

In September 2018, the Company granted a total of 83,791 restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $20.21 per share. Vesting of the restricted stock units was contingent on the achievement of certain performance targets through the first quarter of 2019, subject to the recipient's continuous service through the vesting events. At the date of grant, the Company concluded that the probability of achievement of the performance targets could not be determined until they were achieved, and accordingly, the Company would recognize compensation expense associated with these awards when, and to the extent, the restricted stock units vested in accordance with achievement of the performance targets. As of December 31, 2018, all of the performance targets had been achieved and, consequently, all of the restricted stock units had vested. As a result, $1,693 of stock compensation expense relating to the vesting of restricted stock units was recognized in the Statement of Comprehensive Loss for the year ended December 31, 2018, consisting of $1,217 relating to G&A stock compensation expense and $476 relating to R&D stock compensation expense. In addition, all of the 83,791 restricted stock units were converted to outstanding shares of the Company's common stock as of December 31, 2018.

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**2004 Stock Incentive Plan**

The Company's 2004 Stock Incentive Plan, or the 2004 Plan, as amended, was adopted by the Company's Board of Directors and stockholders. Under the 2004 Plan, the Company has granted stock options to selected officers, employees and consultants of the Company. The Company's Board of Directors administers the 2004 Plan. Options granted under the 2004 Plan have a maximum term of ten years. Options issued generally vest 25% on the first anniversary date of grant and the balance ratably over the next 36 months. Following the effectiveness of the 2014 Plan in January 2014, no additional options or restricted share awards were granted under the 2004 Plan. As of September 30, 2014, the 2004 Plan expired and no further grants of stock options or restricted stock are allowed.

The Company accounts for stock options granted to employees and non-employee members of the Board of Directors in accordance with ASC 718, *Compensation – Stock Compensation*. The Company also occasionally grants stock options to non-employee consultants. Prior to January 1, 2019, the Company used the Black-Scholes option valuation model to re-measure the fair value of all outstanding options that had been granted to non-employee consultants during the vesting period of each tranche in accordance with ASC 505-50. Under ASC 505-50, upon re-measurement of each award, income or expense was recognized during its vesting term. On January 1, 2019, the Company used the Black-Scholes option valuation model to re-measure the fair value of all outstanding unvested options that had been granted to non-employee consultants in accordance with ASU 2018-07 (see Note 2, *Accounting Pronouncements Recently Adopted*).

A summary of the Company's stock option activity related to employees, non-employee members of the Board of Directors and non-employee consultants for the 2019 Plan, the 2014 Plan and the 2004 Plan as of and for the year ended December 31, 2019 is as follows:

| | Number of Shares | Weighted Average Exercise Price | Aggregate Intrinsic Value |
|---|---|---|---|
| Outstanding, December 31, 2018 | 4,004,422 | $ 13.34 | |
| Granted | 1,324,000 | 17.44 | |
| Exercised | (555,847) | 10.98 | |
| Expired | — | — | |
| Forfeited | (322,058) | 15.12 | |
| Outstanding, December 31, 2019 | 4,450,517 | $ 14.73 | $ 10,350 |
| Weighted average remaining contractual life as of December 31, 2019 (in years) | 7.35 | | |
| Options exercisable, December 31, 2019 | 2,407,027 | $ 12.97 | $ 8,733 |
| Weighted average remaining contractual life as of December 31, 2019 (in years) | 6.18 | | |
| Options vested and expected to vest as of December 31, 2019 | 4,450,517 | $ 14.73 | $ 10,350 |
| Weighted average remaining contractual life as of December 31, 2019 (in years) | 7.35 | | |

The total fair value of options vested during the years ended December 31, 2019, 2018 and 2017 was $10,074, $9,023 and $5,303, respectively. The intrinsic value of options exercised during the years ended December 31, 2019, 2018 and 2017 was $5,741, $3,893 and $2,285, respectively.

During the years ended December 31, 2019, 2018 and 2017, the Company granted 1,324,000, 1,197,500 and 1,328,500 stock options, respectively, to employees, non-employee members of the Board of Directors or non-employee consultants under the 2019, 2014 and 2004 plans. The fair values of the stock options granted to those groups were

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estimated using the Black-Scholes option valuation model with the following ranges of assumptions (see Note 2, *Summary of Significant Accounting Policies – Stock-Based Compensation*):

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Risk-free interest rate | 1.55% - 2.62 % | 2.51% - 3.09 % | 1.85% - 2.57 % |
| Expected volatility | 71.1% - 75.2 % | 82.6% - 92.8 % | 75.3% - 84.5 % |
| Expected dividend yield | 0 % | 0 % | 0 % |
| Expected life of employee and Board of Directors' options (in years) | 6.25 | 6.25 | 6.25 |
| Expected life of non-employee options (in years) | — | — | 10 |

The weighted average grant date fair value of options granted to employees, non-employee members of the Board of Directors for their Board service and non-employee consultants during the years ended December 31, 2019, 2018 and 2017 was $11.67, $11.99 and $11.46, respectively.

On January 1, 2019, the Company used the Black Scholes option valuation model to remeasure the fair value of all outstanding unvested options that had been granted to non-employee consultants in accordance with ASU 2018-07. At the end of each fiscal quarter during the years ended December 31, 2018 and 2017, the Company used the Black-Scholes option valuation model to re-measure the fair value of all outstanding options that had been granted to non-employee consultants during the vesting period of each tranche in accordance with ASC 505-50. The range of assumptions used by the Company on January 1, 2019 and during the years ended December 31, 2018 and 2017 are as follows:

| | January 1, | December 31, | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Risk-free interest rate | 2.59% - 2.62% | 1.82% - 3.02% | 1.28% - 2.39% |
| Expected volatility | 58.9% - 84.6% | 58.2% - 101.0% | 74.6% - 87.3% |
| Expected dividend yield | 0% | 0% | 0% |
| Expected life of non-employee options (in years) | 0.81 - 8.19 | 0.25 - 8.94 | 0.62 - 9.94 |

The weighted average fair value of outstanding options that had been granted to nonemployee consultants during the years ended December 31, 2018 and 2017 was $8.74 and $10.16, respectively. There were no options granted to nonemployee consultants during the year ended December 31, 2019.

During the years ended December 31, 2019, 2018 and 2017, the Company recognized compensation expense relating to stock options as follows:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Research and development | $ 5,206 | $ 3,919 | $ 2,433 |
| General and administrative | 5,094 | 4,482 | 3,897 |
| Total stock option expense | $ 10,300 | $ 8,401 | $ 6,330 |

The following were excluded from the table above as they are not related to stock options: compensation expense for i) the issuance of common stock relating to the consulting agreement for $197 in G&A expense for the year ended December 31, 2019; ii) the vesting of executives' restricted stock units for $604 and $476 in R&D expense for the years ended December 31, 2019 and 2018, respectively, and $1,180 and $1,217 in G&A expense for the years ended December 31, 2019 and 2018, respectively; and iii) compensation expense relating to the Board of Directors' restricted stock units for $287 in G&A expense for the year ended December 31, 2019.

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In October 2018, the Company modified the terms of its former Chief Medical Officer's outstanding Stock Awards to accelerate 50% of the unvested shares underlying his outstanding stock options immediately as of the modification date, and specify that the remainder of the unvested shares would vest monthly through the date of termination of his continuous service to the Company as a Consultant. As of the modification date, the Company entered into a consulting agreement with the former Chief Medical Officer under which he provided continuous service to the Company as a Consultant by providing transition services and other services upon request by the Company. Pursuant to the terms of the separation and consulting agreement, such Stock Awards continued to vest under their original vesting conditions as long as he provided continuous service to the Company (including as a consultant). The term of his consulting agreement ended on May 31, 2019.

In August 2017, the Company modified the terms of its former Chief Financial Officer's outstanding Stock Awards to (1) accelerate 50% of the unvested shares underlying his outstanding Stock Awards immediately as of the modification date and specify that the remainder will vest monthly through the date of termination of his continuous service to the Company; and (2) extend the period during which his outstanding Stock Awards may be exercised through the six-month anniversary of the date of termination of his continuous service to the Company. As of the modification date, the Company entered into a consulting agreement with the former Chief Financial Officer under which he provided continuous service to the Company by assisting with the transition of his role to the Company's Chief Financial Officer. Pursuant to the terms of the 2014 Plan and his outstanding Stock Awards, such Stock Awards continued to vest under their original vesting conditions as long as he provided continuous service to the Company (including as a consultant). The term of his consulting agreement ended on February 15, 2018.

The Company determined that the acceleration of vesting for Stock Awards in 2018 and 2017 that would have vested based on their original vesting terms through the term of the consulting services were Type 1 modifications pursuant to ASC 718, *Compensation – Stock Compensation*, because those Stock Awards would have vested whether or not the vesting of those Stock Awards had been accelerated. However, acceleration of vesting for the remaining Stock Awards was a Type 3 modification pursuant to ASC 718 because absent the modification terms, those Stock Awards would have been forfeited as of the last day that the former Chief Medical Officer and Chief Financial Officer provided continuous service as a consultant.

During the year ended December 31, 2018, with respect to these modifications for the former Chief Medical Officer, the Company recognized $520 of compensation expense, including expense based on marking to market the fair value of the modified Stock Awards in accordance with ASC 505-50, which is included in Research and development expense in the total compensation expense table above.

During the years ended December 31, 2018 and 2017, with respect to these modifications for the former Chief Financial Officer, the Company recognized $96 and $537 of compensation expense, respectively, including expense based on marking to market the fair value of the modified Stock Awards in accordance with ASC 505-50, which is included in General and administrative expense in the total compensation expense table above.

As of December 31, 2019, the total compensation expense relating to unvested options granted to employees, non-employee members of the Board of Directors and non-employee consultants that had not yet been recognized was $22,216, which is expected to be realized over a weighted average period of 2.74 years. The Company will issue shares upon exercise of options from common stock reserved.

The Company does not expect to realize any tax benefits from its stock option activity or the recognition of stock-based compensation expense because the Company currently has net operating losses and has a full valuation allowance against its deferred tax assets. Accordingly, no amounts related to excess tax benefits have been reported in cash flows from operations or cash flows from financing activities for the years ended December 31, 2019, 2018 and 2017.

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## 14. Income Taxes

The Company's benefit from income taxes is as follows:

| | December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Current: | | | |
| Federal | $ — | $ — | $ — |
| State | (816) | (389) | (204) |
| | (816) | (389) | (204) |
| Deferred: | | | |
| Federal | — | — | — |
| State | — | — | — |
| | — | — | — |
| Benefit from income taxes | $ (816) | $ (389) | $ (204) |

The Company's tax benefits relate to state R&D tax credits exchanged for cash. The State of Connecticut provides companies with the opportunity to exchange certain R&D credit carryforwards for cash in exchange for foregoing the carryforward of the R&D credit. The program provides for such exchange of the R&D credits at a rate of 65% of the annual R&D credit, as defined.

A reconciliation of income taxes computed using the U.S. federal statutory rate to that reflected in operations is as follows:

| | December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Income taxes using U.S. federal statutory rate | 21.00 % | 21.00 % | 34.00 % |
| State income taxes, net of federal benefit | (1.99)% | 6.82 % | 5.33 % |
| Tax Cuts and Jobs Act | 0.00 % | 0.00 % | (44.43)% |
| Impact of R&D tax credit on effective tax rate | 4.34 % | 3.48 % | 3.25 % |
| Stock option shortfalls and cancellations | (0.17)% | (0.43)% | 0.21 % |
| Permanent items and other | 0.36 % | (0.15)% | (0.56)% |
| Change in valuation allowance | (22.76)% | (31.76)% | 2.55 % |
| Provision to return | (0.02)% | 0.03 % | 0.00 % |
| Non-taxable revenue | 0.00 % | 1.54 % | 0.00 % |
| | 0.76 % | 0.53 % | 0.35 % |

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

| | December 31, | |
|---|---|---|
| | 2019 | 2018 |
| Valuation allowance | $ (114,136) | $ (89,815) |
| | | |
| Net operating loss carryforwards | 84,608 | 73,578 |
| Federal and state tax credits | 16,624 | 11,108 |
| Deferred revenue | 5,994 | 1,111 |
| Stock-based compensation expense | 4,481 | 3,605 |
| Other | 3,409 | 420 |
| Deferred tax assets | 115,116 | 89,822 |
| | | |
| Other | (980) | (7) |
| Deferred tax liabilities: | (980) | (7) |
| | | |
| Net deferred tax asset: | $ — | $ — |

A 100% valuation allowance has been recorded on the deferred tax asset as of December 31, 2019 and 2018 because management believes it is more likely than not that the asset will not be realized. The change in the valuation allowance during 2019 and 2018 was an increase of $24,321 and $23,642, respectively.

The Company applies the provisions of ASC 740, *Income Taxes*, 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 of 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 income tax expense.

At December 31, 2019, the Company had federal and state net operating loss carryforwards of $349,525 and $189,157, respectively. The federal and state tax loss carryforwards will begin to expire in 2026 and 2027, respectively, unless previously utilized. The federal net operating losses arising in 2018 and forward have an unlimited carryforward period, however will only offset 80% of taxable income in a carryforward year. The federal losses may also be subject to limitation pursuant to Internal Revenue Code section 382. The Company also had federal and state R&D tax credit carryforwards of $15,274 and $1,448, respectively. The federal credits will begin expiring in 2025 unless previously utilized. The Connecticut credit carryforwards have no expiration period. Because of the net operating loss and research credit carryforwards, tax years 2006 through 2019 remain open to U.S. federal and state tax examinations.

On December 22, 2017, the United States enacted the Tax Cuts and Jobs Act, or the TCJA. The TCJA, which is also commonly referred to as "U.S. tax reform", significantly changes U.S. corporate income tax laws by, among other provisions, reducing the maximum U.S. corporate income tax rate from 35% to 21% starting in 2018. As of December 31, 2019 and 2018, the Company did not have any foreign subsidiaries and the international aspects of the TCJA were not applicable.

On December, 22, 2017, SAB 118 was issued by the SEC due to the complexities involved in accounting for the TCJA. SAB 118 requires the Company to include in its financial statements a reasonable estimate of the impact of the TCJA on earnings to the extent such estimate has been determined. The Company finalized its accounting for the TCJA as of December 31, 2018, which resulted in insignificant adjustments.

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## 15. Net Loss per Share

The Company computes net loss per share in accordance with ASC 260-10, *Earnings per Share* (see Note 2, *Significant Accounting Policies – Income (Loss) per Share*).

The denominators used in the net loss per share computations are as follows:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| **Basic:** | | | |
| Weighted average common shares outstanding | 42,669,333 | 35,892,786 | 31,202,842 |
| **Diluted:** | | | |
| Weighted average common shares outstanding - Basic | 42,669,333 | 35,892,786 | 31,202,842 |
| Common stock options* | — | — | — |
| Denominator for diluted net loss per share | 42,669,333 | 35,892,786 | 31,202,842 |

* No amounts were considered as their effects would be anti-dilutive.

Basic and diluted net loss per share are computed as follows:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Net loss | $ (106,373) | $ (74,013) | $ (58,125) |
| Weighted-average common shares outstanding: | | | |
| Basic and Diluted | 42,669,333 | 35,892,786 | 31,202,842 |
| Net loss per share, Basic and Diluted | $ (2.49) | $ (2.06) | $ (1.86) |

As of December 31, 2019, 2018 and 2017, 4,450,517, 4,004,422 and 3,492,141 stock options, respectively, were outstanding, which could potentially dilute basic earnings per share in the future, but were not included in the computation of diluted net loss per share because to do so would have been anti-dilutive. In addition, 104,168 unvested restricted stock units issued to executive officers that were outstanding at December 31, 2019 were also not included in the computation of diluted net loss per share because to do so would have been anti-dilutive. The 36,666 and 74,166 restricted stock units that vested and were settled in shares of common stock in December 2019 and May 2019, respectively, were included in the computation of basic and diluted net loss per share for the year ended December 31, 2019. The 24,000 restricted stock units granted in June 2019 to the non-employee members of the Board of Directors were also not included in the computation of diluted net loss per share because to do so would have been anti-dilutive (see Note 13, *Stock-Based Compensation*).

## 16. Employee Benefit Plan

In February 2006, the Company adopted a defined contribution retirement plan that complies with Section 401(k) of the Internal Revenue Code. All employees over the age of 21 are eligible to participate in the plan at the beginning of the calendar quarter after three consecutive months of service. Employees are able to defer a portion of their pay into the plan on the first day of the quarter on or after the day all age and service requirements have been met. All eligible employees receive an employer contribution equal to 3% of their salary up to the annual IRS limit. During the years ended December 31, 2019, 2018 and 2017, employer contributions to the plan were $279, $198 and $174, respectively.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

## 17. Commitments and Contingencies

*License Agreement with Enteris Biopharma, Inc.*

On August 20, 2019, the Company entered into the Enteris License Agreement, pursuant to which Enteris granted to the Company a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

As consideration for the licensed rights under the Enteris License Agreement, the Company paid an upfront fee equal to $8,000, consisting of $4,000 in cash and $4,000 in shares of the Company's common stock pursuant to the Purchase Agreement (see Note 9, *Stockholders' Equity*). As a result, the Company recognized R&D expense of $8,000 related to the Enteris License Agreement during the year ended December 31, 2019.

The Company is also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low-single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, the Company has the right, but not the obligation, to terminate its obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. Subject to certain conditions, the Company may elect to pay 50% of the lump sum due under the Royalty Buyout in shares of the Company's common stock pursuant to the Purchase Agreement. During the year ended December 31, 2019, no milestone payments or royalties were paid to Enteris by the Company.

The Enteris License Agreement will expire on a country-by-country, licensed product-by-licensed product basis upon the later of (1) the expiration (or invalidation) of all valid claims in licensed patent rights that cover such product in such country, (2) the end of the calendar quarter in which generic competition (as defined in the Enteris License Agreement) occurs for such product in such country and (3) ten years from the first commercial sale of such product.

Either party may terminate the Enteris License Agreement upon written notice if the other party has failed to remedy a material breach within 60 days (or 30 days in the case of a material breach of a payment obligation). Enteris may terminate the Enteris License Agreement upon 30 days' written notice to the Company if the Company or any of its affiliates formally challenge the validity of any licensed patent rights or assists a third party in doing so. The Company may terminate the Enteris License Agreement for any reason or no reason (a) prior to receipt of first regulatory approval for a licensed product in the United States for any indication upon 30 days' prior written notice to Enteris or (b) on or after receipt of first regulatory approval for a licensed product in the United States for any indication upon 60 days' prior written notice to Enteris.

*Manufacturing Agreement with Patheon UK Limited*

On July 8, 2019, the Company entered into a Master Manufacturing Services Agreement, or MSA, with Patheon UK Limited, or Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to the Company for the drug products specified by the Company from time to time. Pursuant to the MSA, the Company has agreed to order from Patheon at least a certain percentage of its commercial requirements for a product under a related Product Agreement. Each Product Agreement that the Company may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

The MSA has an initial term ending December 31, 2023, and will automatically renew after the initial term for successive terms of two years each if there is a Product Agreement in effect, unless either party gives notice of its intention to terminate the MSA at least 18 months prior to the end of the then current term.

Either party may terminate the MSA or a Product Agreement upon written notice if the other party (1) has failed to remedy a material breach within a specified time or (2) is declared insolvent or bankrupt, voluntarily files a petition of bankruptcy or assigns such agreement for the benefit of creditors. The Company may terminate a Product Agreement (a) upon 90 days' prior written notice if any governmental agency takes any action that prevents the Company from selling the relevant product in the relevant territory, (b) upon six months' prior written notice if it does not intend to order manufacturing services due to a product's discontinuance in the market, or (c) upon 90 days' prior written notice if it determines that the manufacture or supply of a product likely infringes third-party rights. Patheon may terminate the MSA or a Product Agreement (i) upon six months' prior written notice if the Company assigns such agreement to an assignee that is unacceptable to Patheon for certain reasons, or (ii) upon 30 days' prior written notice if, after the first year of commercial sales, the Company forecasts zero volume for 12 months.

The MSA contains, among other provisions, customary representations and warranties by the parties, a grant to Patheon of certain limited license rights to the Company's intellectual property in connection with Patheon's performance of the services under the MSA, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions.

On July 8, 2019, and July 9, 2019, the Company entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of CR845/difelikefalin injection, the Company's lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of CR845/difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from active pharmaceutical ingredient supplied by the Company. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product.

*Leases*

In December 2015, the Company entered into a lease agreement, or the Stamford Lease, for office space in Stamford, Connecticut, or the Premises, for the purpose of relocating its headquarters. The initial term of the Stamford Lease commenced in May 2016, or the Commencement Date, and ends in November 2023 and is renewable for one five-year term.

The Stamford Lease requires monthly lease payments, including rent escalations and rent holidays, during the initial lease term. The Company began to make rental payments from the Commencement Date. Prior to January 1, 2019, the Company recorded monthly rent expense on a straight-line basis from March 2016, upon taking possession of the Premises, through December 31, 2018. As of December 31, 2018, the balance of deferred lease obligation, representing the difference between cash rent paid and straight-line rent expense, was $864.

As of the Commencement Date, the Stamford Lease landlord had made tenant improvements of $1,094 to the leased premises. Such amount was included in Property and equipment, net and in Deferred lease obligation as of December 31, 2018. The portion of Deferred lease obligation that is related to tenant improvements was being amortized as a reduction to rent expense over the same term as rent expense. As of December 31, 2018, the balance of Deferred lease obligation related to tenant improvements was $698.

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

Total rent expense under the Stamford Lease was $974 and $935 for the years ended December 31, 2018 and 2017, respectively.

In connection with the signing of the Stamford Lease, the Company entered into a standby letter of credit agreement which serves as a security deposit for the Premises. The standby letter of credit is automatically renewed annually through November 2023. This standby letter of credit is secured with restricted cash in a money market account (refer to Note 7, *Restricted Cash*).

On January 1, 2019, the Company adopted ASC 842 (see Note 2 – *Basis of Presentation: Accounting Pronouncements Recently Adopted*). Under ASC 842, since the Company adopted the practical expedients not to re-evaluate whether a contract is or contains a lease and to maintain the lease classification under ASC 840, the Stamford Lease continues to be accounted for as an operating lease.

Upon adoption of ASC 842, the Company was required to establish an operating lease ROU asset and operating lease liability for the Stamford Lease. In establishing the ROU asset, the operating lease liability of $5,198 was reduced by lease incentives relating to tenant improvements of $698 and deferred lease obligation of $864, which were outstanding on December 31, 2018.

Under ASC 842, lease expense is recognized on a straight-line basis over the lease term. As a result, $937 of operating lease cost, or lease expense, was recognized for the year ended December 31, 2019, consisting of $656 relating to R&D lease expense and $281 relating to G&A lease expense.

Other information related to the Stamford Lease was as follows:

| | Year Ended December 31, 2019 |
|---|---|
| Cash paid for amounts included in the measurement of lease liability: | |
| Operating cash outflows relating to operating lease | $ 1,215 |
| ROU assets obtained in exchange for new operating lease liabilities | $ 3,636 |
| Remaining lease term-operating lease (years) | 3.9 |
| Discount rate - operating lease | 7.0 % |

**CARA THERAPEUTICS, INC.**

**NOTES TO FINANCIAL STATEMENTS**
**(amounts in thousands, except share and per share data)**

Future minimum lease payments under non-cancellable operating leases, as well as a reconciliation of these undiscounted cash flows to the operating lease liability as of December 31, 2019, were as follows:

| | |
|---|---|
| Year Ending December 31, | |
| 2020 | $ 1,239 |
| 2021 | 1,264 |
| 2022 | 1,288 |
| 2023 | 1,164 |
| 2024 | — |
| Total future minimum lease payments, undiscounted | 4,955 |
| Less imputed interest | (636) |
| Total | $ 4,319 |

| | |
|---|---|
| Operating lease liability reported as of December 31, 2019: | |
| Operating lease liability - current | $ 967 |
| Operating lease liability - non-current | 3,352 |
| Total | $ 4,319 |

**18. Legal Matters**

From time to time, the Company may become subject to arbitration, litigation or claims arising in the ordinary course of its business. The Company is not currently a party to any arbitration or legal proceeding that, if determined adversely to the Company, would have a material adverse effect on its business, operating results or financial condition. The results of any future claims or proceedings cannot be predicted with certainty, and regardless of the outcome, litigation can have an adverse impact on the Company because of defense and settlement costs, diversion of management resources and other factors.

**19. Quarterly Results of Operations (Unaudited)**

The following tables contain selected financial data for each quarter of the years ended December 31, 2019 and 2018. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for each quarter of the years ended December 31, 2019 and 2018. The operating results for any period are not necessarily indicative of results for any future periods.

| | Year Ended December 31, 2019 | | | |
|---|---|---|---|---|
| | First Quarter | Second Quarter | Third Quarter | Fourth Quarter |
| Revenues | $ 4,382 | $ 5,208 | $ 5,785 | $ 4,511 |
| Net loss - Basic and Diluted | (21,960) | (22,960) | (32,842) | (28,611) |
| Loss per share - Basic and Diluted | $ (0.56) | $ (0.58) | $ (0.74) | $ (0.61) |

| | Year Ended December 31, 2018 | | | |
|---|---|---|---|---|
| | First Quarter | Second Quarter | Third Quarter | Fourth Quarter |
| Revenues | $ — | $ 2,874 | $ 5,062 | $ 5,533 |
| Net loss - Basic and Diluted | (16,767) | (17,194) | (19,400) | (20,652) |
| Loss per share - Basic and Diluted | $ (0.51) | $ (0.52) | $ (0.51) | $ (0.52) |

**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 Principal Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2019. Based on such evaluation, our Chief Executive Officer and Principal Financial Officer have concluded that, as of December 31, 2019, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC, and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosures.

*Management's Report on Internal Control over Financial Reporting*

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management utilized the criteria established in the Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) to conduct an assessment of the effectiveness of our internal control over financial reporting as of December 31, 2019. Based on the assessment, management has concluded that, as of December 31, 2019, our internal control over financial reporting was effective.

Ernst & Young LLP, an independent registered public accounting firm, has audited the effectiveness of our internal control over financial reporting as of December 31, 2019, as stated in their attestation report, which is included in Part II Item 8 of this Annual Report.

*Changes in Internal Control Over Financial Reporting*

There was no change in our internal control over financial reporting that occurred during the quarter ended December 31, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

*Limitations on Controls and Procedures*

Management, including our Chief Executive Officer and Principal Financial Officer, recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost benefit relationship of possible controls and procedures. Because of the inherent limitations in all control systems, no evaluation of controls and procedures can provide absolute assurance that all control issues and instances of fraud, if any, within Cara have been detected.

**Item 9B.** ***Other Information.***

None.

## PART III

**Item 10.** ***Directors, Executive Officers and Corporate Governance.***

The information required by this item will be set forth under the captions “Executive Officers and Directors of Cara” and “Board of Directors and Corporate Governance” in our Definitive Proxy Statement 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 will be set forth under the captions “Executive Compensation” and “Board of Directors and Corporate Governance” in our Definitive Proxy Statement 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 will be set forth under the captions “Security Ownership of Certain Beneficial Owners and Management” and “Securities Authorized for Issuance under Equity Compensation Plans” in our Definitive Proxy Statement with respect to our 2020 Annual Meeting of Stockholders and is incorporated by reference.

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

The information required by this item will be set forth under the captions “Transactions with Related Persons” and “Board of Directors and Corporate Governance” in our Definitive Proxy Statement with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

**Item 14.** ***Principal Accountant Fees and Services*****.**

The information required by this item will be set forth under the caption “Independent Registered Public Accounting Firm’s Fees” in our Definitive Proxy Statement with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

## PART IV

**Item 15.** ***Exhibits, Financial Statement Schedules*****.**

(a) We have filed the following documents as part of this Annual Report on Form 10-K:

**(1) Financial Statements of Cara Therapeutics, Inc.**

INDEX TO FINANCIAL STATEMENTS

**(2) Financial Statement Schedules**

All schedules for which provision is made in the applicable accounting regulations of the SEC which are not included with this additional financial data have been omitted because they are not applicable or the required information is shown in the Financial Statements or Notes included in Item 8. *Financial Statements and Supplementary Data*.

**(3) List of Exhibits**

| | | Incorporated by Reference | | | |
|---|---|---|---|---|---|
| **Exhibit No.** | **Description of Exhibit** | **Form** | **File No.** | **Exhibit No.** | **Date Filed** |
| 3.1 | Amended and Restated Certificate of Incorporation. | 8-K | 001-36279 | 3.1 | February 7, 2014 |
| 3.2 | Amended and Restated Bylaws. | 8-K | 001-36279 | 3.2 | February 7, 2014 |
| 4.1 | Form of Common Stock Certificate. | S-1/A | 333-192230 | 4.1 | January 17, 2014 |
| 4.2# | Common Stock Purchase Agreement, dated August 20, 2019, by and among the Registrant, Enteris Biopharma, Inc. and EBP Holdco LLC. | S-3ASR | 333-233666 | 4.3 | September 9, 2019 |
| 4.3† | Description of Securities. | | | | |
| 10.1+ | Form of Indemnity Agreement. | S-1/A | 333-192230 | 10.1 | January 17, 2014 |
| 10.2+ | 2004 Stock Incentive Plan, as amended, and forms of Stock Option Agreement thereunder. | S-1 | 333-192230 | 10.2 | November 8, 2013 |
| 10.3+ | 2014 Equity Incentive Plan. | S-1/A | 333-192230 | 10.3 | January 17, 2014 |
| 10.3.1 | Form of Stock Option Agreement under 2014 Equity Incentive Plan. | S-1/A | 333-192230 | 10.3.1 | January 17, 2014 |
| 10.3.2 | Form of Restricted Stock Unit Award under 2014 Equity Incentive Plan. | S-1/A | 333-192230 | 10.3.2 | January 17, 2014 |
| 10.4 | Fourth Amended and Restated Investors Rights Agreement dated April 25, 2013 among the Registrant and certain of its stockholders, as amended. | S-1 | 333-192230 | 10.5 | November 8, 2013 |
| 10.5* | License Agreement dated April 4, 2013 by and between the Registrant and Maruishi Pharmaceutical Co., Ltd. | S-1 | 333-192230 | 10.7 | November 8, 2013 |
| 10.6* | License and API Supply Agreement effective as of April 16, 2012 by and between the Registrant and Chong Kun Dang Pharmaceutical Corp. | S-1 | 333-192230 | 10.8 | November 8, 2013 |

| | | | | | |
|---|---|---|---|---|---|
| 10.7 | Amendment to License and API Supply Agreement effective as of May 1, 2012 by and between the Registrant and Chong Kun Dang Pharmaceutical Corp. | S-1 | 333-192230 | 10.9 | November 8, 2013 |
| 10.8+ | Employment Agreement with Derek Chalmers. | 8-K | 001-36279 | 10.1 | February 7, 2014 |
| 10.9+ | Employment Agreement with Frédérique Menzaghi. | 8-K | 001-36279 | 10.2 | February 7, 2014 |
| 10.10+ | Employment Agreement with Joana Goncalves. | 10-K | 001-36279 | 10.11 | March 12, 2019 |
| 10.11+ | Amended and Restated Non-Employee Director Compensation Policy. | 10-Q | 001-36279 | 10.1 | August 7, 2019 |
| 10.12 | Lease Agreement dated December 21, 2015 between the Registrant and Four Stamford Plaza Owner L.L.C. | 8-K | 001-36279 | 10.1 | December 23, 2015 |
| 10.13* | License Agreement by and between Cara Therapeutics, Inc. and Vifor Fresenius Medical Care Renal Pharma Ltd. | 10-Q | 001-36279 | 10.1 | August 7, 2018 |
| 10.14# | Master Manufacturing Services Agreement between the Registrant and Patheon UK Limited and related Product Agreements | 10-Q | 001-36279 | 10.2 | August 7, 2019 |
| 10.15# | Non-Exclusive License Agreement, dated August 20, 2019, between the Registrant and Enteris Biopharma, Inc. | 10-Q | 001-36279 | 10.1 | November 5, 2019 |
| 10.16+ | 2019 Inducement Plan. | 8-K | 001-36279 | 10.1 | November 20, 2019 |
| 10.17 | Form of Stock Option Grant Notice under 2019 Inducement Plan | 8-K | 001-36279 | 10.2 | November 20, 2019 |
| 10.18 | Form of Restricted Stock Unit Notice under 2019 Inducement Plan | 8-K | 001-36279 | 10.3 | November 20, 2019 |
| 23.1† | Consent of Ernst & Young, LLP, independent registered public accounting firm. | | | | |
| 24.1† | Power of Attorney (included on signature page). | | | | |
| 31.1† | Certification of Chief Executive Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934. | | | | |

| | |
|---|---|
| 31.2† | Certification of Principal Financial Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934. |
| 32.1†** | Certifications of Chief Executive Officer and Principal Financial Officer of Cara Therapeutics, Inc. pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |
| 101.CAL | XBRL Taxonomy Extension Calculation Linkbase. |
| 101.INS | XBRL Instance Document. |
| 101.LAB | XBRL Taxonomy Extension Label Linkbase |
| 101.PRE | XBRL Taxonomy Extension Presentation Linkbase. |
| 101.SCH | XBRL Taxonomy Extension Schema Linkbase |
| 101.DEF | XBRL Taxonomy Extension Definition Linkbase Document. |

+ indicates management contract or compensatory plan.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

# Portions of this exhibit (indicated by asterisks) have been omitted because the Registrant has determined they are not material and would likely cause competitive harm to the Registrant if publicly disclosed.

† Filed herewith.

** This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

**SIGNATURES**

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on this 27th day of February 2020.

CARA THERAPEUTICS, INC.
By: /s/ DEREK CHALMERS
Name: Derek Chalmers, Ph.D., D.Sc.
Title: President and Chief Executive Officer

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Derek Chalmers, Ph.D., D.Sc. and Scott Terrillion, and each of them, as his true and lawful attorneys-in-fact and agents, with full power of substitution for him, and in his name in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the U.S. Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and either of them, his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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

| Signature | Title | Date |
|---|---|---|
| /s/ DEREK CHALMERS<br>Derek Chalmers, Ph.D., D.Sc. | President, Chief Executive Officer and Director<br>(*Principal Executive Officer)* | February 27, 2020 |
| /s/ RICHARD MAKARA<br>Richard Makara | Vice President, Head of Accounting & Controller<br>*(Principal Financial and Accounting Officer)* | February 27, 2020 |
| /s/ MARTIN VOGELBAUM<br>Martin Vogelbaum | Director | February 27, 2020 |
| /s/ HARRISON M. BAINS, JR.<br>Harrison M. Bains, Jr. | Director | February 27, 2020 |
| /s/ JEFFREY IVES<br>Jeffrey Ives, Ph.D. | Director | February 27, 2020 |
| /s/ CHRISTOPHER POSNER<br>Christopher Posner | Director | February 27, 2020 |

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

As of December 31, 2019, Cara Therapeutics, Inc. had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended, or the Exchange Act: our common stock, par value $0.001 per share. References herein to the terms "we," "us" and "our" refer to Cara Therapeutics, Inc.

The following description of our capital stock is a summary and does not purport to be complete. It is subject to, and qualified in its entirety by reference to, the applicable provisions of our amended and restated certificate of incorporation and our amended and restated bylaws, which are filed as exhibits to our Annual Report on Form 10-K, of which this Exhibit 4.3 is a part, and are incorporated by reference herein. We encourage you to read our amended and restated certificate of incorporation, our amended and restated bylaws and the applicable provisions of the Delaware General Corporation Law, or the DGCL, for more information.

## General

Under our amended and restated certificate of incorporation, we are authorized to issue up to 100,000,000 shares of common stock, par value $0.001 per share, and up to 5,000,000 shares of preferred stock, par value $0.001 per share. The shares of common stock currently outstanding are fully paid and nonassessable. No shares of preferred stock are currently outstanding.

Additional shares of authorized common stock may be issued, as authorized by our board of directors, or the Board, from time to time, without stockholder approval, except as may be required by applicable stock exchange requirements. The rights of the holders of our common stock are subject to, and may be adversely affected by, the rights of holders of shares of any preferred stock that we may designate and issue in the future.

Our common stock is listed on the Nasdaq Global Market under the symbol "CARA."

## No Preemptive, Redemption or Conversion Rights

The common stock is not redeemable, is not subject to sinking fund provisions, does not have any conversion rights and is not subject to call. Holders of shares of common stock have no preemptive rights.

## Voting Rights

Each outstanding share of common stock entitles the holder thereof to one vote on each matter properly submitted to a vote. Holders of shares of common stock do not have cumulative voting rights in the election of directors.

## Dividend Rights

Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of our common stock are entitled to receive ratably such dividends as may be declared by the Board out of legally available funds.

## Liquidation Rights

Upon our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock.

**Board of Directors**

Our Board is divided into three classes. The number of directors authorized to serve on the Board at any time will be fixed exclusively by a resolution adopted by a majority of the Board.

**Antitakeover Effects of Provisions of Charter Documents and Delaware Law**

***Charter Documents***. Our amended and restated certificate of incorporation and bylaws include a number of provisions that may have the effect of deterring hostile takeovers or delaying or preventing changes in control or management of our company. First, the Board is classified into three classes of directors. Under Delaware law, directors of a corporation with a classified board may be removed only for cause unless the corporation's certificate of incorporation provides otherwise. Our amended and restated certificate of incorporation provides that any director may be removed with cause by the affirmative vote of the holders of at least 66 2/3% of the voting power of all then-outstanding shares of our capital stock entitled to vote generally at an election of directors. Our amended and restated certificate of incorporation does not include a provision for cumulative voting for directors. Under cumulative voting, a minority stockholder holding a sufficient percentage of a class of shares may be able to ensure the election of one or more directors. In addition, our amended and restated certificate of incorporation provides that all stockholder action must be effected at a duly called meeting of stockholders and not by a consent in writing. Pursuant to our amended and restated bylaws, a special meeting of the stockholders may be called only by the Chairperson of the Board, the Chief Executive Officer, or the Board. Finally, our amended and restated bylaws establish procedures, including advance notice procedures, with regard to the nomination of candidates for election as directors and stockholder proposals. These and other provisions of our amended and restated certificate of incorporation and bylaws and Delaware law could discourage potential acquisition proposals and could delay or prevent a change in control or management of our company.

***Delaware Takeover Statute***. We are subject to Section 203 of the DGCL, which regulates acquisitions of some Delaware corporations. Section 203 generally prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years following the date of the transaction in which the person became an interested stockholder, subject to certain exceptions.

***Choice of Forum***. Our amended and restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for (A) any derivative action or proceeding brought on our behalf (B) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee to us or our stockholders; (C) any action asserting a claim against us arising pursuant to any provision of the DGCL, our certificate of incorporation or our bylaws; or (D) any action asserting a claim against us governed by the internal affairs doctrine.

**EXHIBIT 23.1**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3ASR No. 333-233666) of Cara Therapeutics, Inc.

(2) Registration Statement (Form S-3 No. 333-230333) of Cara Therapeutics, Inc.

(3) Registration Statement (Form S-3 No. 333-216657) of Cara Therapeutics Inc.

(4) Registration Statement (Form S-8 No. 333-234800) of Cara Therapeutics, Inc., pertaining to the Cara Therapeutics, Inc. 2019 Inducement Plan

(5) Registration Statement (Form S-8 No. 333-230335) of Cara Therapeutics, Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.

(6) Registration Statement (Form S-8 No. 333-223726) of Cara Therapeutics, Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.

(7) Registration Statement (Form S-8 No. 333-216606) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.

(8) Registration Statement (Form S-8 No. 333-210096) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.

(9) Registration Statement (Form S-8 No. 333-203057) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc., and

(10) Registration Statement (Form S-8 No. 333-193905) pertaining to the 2004 Stock Incentive Plan, as amended, and 2014 Equity Incentive Plan;

of our reports dated February 27, 2020, with respect to the financial statements of Cara Therapeutics, Inc. and the effectiveness of internal control over financial reporting of Cara Therapeutics, Inc. included in this Annual Report (Form 10-K) of Cara Therapeutics Inc., for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Stamford, Connecticut
February 27, 2020

**EXHIBIT 31.1**

**Certification of Chief Executive Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002**

I, Derek Chalmers, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cara 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter 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: February 27, 2020

By: /s/ Derek Chalmers
DEREK CHALMERS, Ph.D., D.Sc.
CHIEF EXECUTIVE OFFICER

**EXHIBIT 31.2**

**Certification of Principal Financial Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002**

I, Richard Makara, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cara 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter 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: February 27, 2020

By: /s/ Richard Makara
RICHARD MAKARA
VP, HEAD OF ACCOUNTING & CONTROLLER
(*PRINCIPAL FINANCIAL OFFICER*)

**EXHIBIT 32.1**

**CERTIFICATIONS OF**
**CHIEF EXECUTIVE OFFICER AND PRINCIPAL FINANCIAL OFFICER**
**OF CARA THERAPEUTICS, INC.**
**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 Cara Therapeutics, Inc. (the "Company") for the year ended December 31, 2019, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Derek Chalmers, Ph.D., D.Sc., as Chief Executive Officer of the Company, and Richard Makara, as VP, Head of Accounting & Controller of the Company, each 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 the best of his knowledge, based upon a review of the Report:

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

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

/s/ DEREK CHALMERS
Name: Derek Chalmers, Ph.D., D.Sc.
Title: Chief Executive Officer
Date: February 27, 2020

/s/ RICHARD MAKARA
Name: Richard Makara
Title: VP, Head of Accounting & Controller
(*Principal Financial Officer*)
Date: February 27, 2020