Cara Therapeutics, Inc.
Form 10-K
March 12, 2019

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, 2018

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

107 Elm Street, 9th Floor

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	Name of each exchange on which registered
Common Stock, par value $0.001 per share	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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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 $561,082,035. For purposes of this calculation, shares of common stock held by directors and officers and their affiliated entities at June 30, 2018 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 March 5, 2019 was 39,547,558.

CARA THERAPEUTICS, INC.

2018 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,” “p “project,” “potential,” “should,” “will,” or “would,” and or the negative of these terms, or other comparable terminology intend 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, including our clinical trial programs for KORSUVA™ (CR845/difelikefalin) injection in chronic kidney disease associated pruritus, or CKD-aP, and Oral KORSUVA (CR845/difelikefalin) in CKD-aP, and chronic liver disease associated pruritus, or CLD-aP, and other investigational indications, and the reporting of clinical trial results;
- the potential regulatory development pathway for KORSUVA (CR845/difelikefalin) injection in CKD-aP and CR845/difelikefalin injection in acute post-operative setting;
- our plans to develop and commercialize KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) and our other 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 markets as well as post-operative care markets, and for our other product candidates and our ability to serve those markets;
- our ability to obtain and maintain regulatory approval of our product candidates, including intravenous, or I.V., and Oral CR845/difelikefalin, and the labeling under any approval we may obtain;
- the anticipated commercial launch of our lead product candidate, KORSUVA (CR845/difelikefalin) injection;
- 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;
- the rate and degree of market acceptance of any approved products;
- 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.

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 with a primary focus on pruritus as well as pain by selectively targeting peripheral kappa opioid receptors. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), a first-in-class kappa opioid receptor agonist that targets the body's peripheral nervous system, as well as certain immune cells.

In 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, and is currently being investigated in Phase 3 trials in hemodialysis patients with 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 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.

Recent Developments

Chief Medical Officer

Effective October 22, 2018, we appointed Joana Goncalves, M.D. as our new Chief Medical Officer, or CMO. Prior to joining Cara, Dr. Goncalves was the Vice President, Global Medical Affairs for Dermatology and Neurology at Celgene Corporation. Previously, she held various positions at LEO Pharma Inc., the U.S. subsidiary of Leo Pharma A/S and at Novartis Pharmaceuticals. Dr. Goncalves received her M.D. from The University of Cape Town, South Africa. On October 22, 2018, we entered into a Separation and Consulting Agreement with Joseph Stauffer, D.O., our former CMO, pursuant to which he will provide consulting services to us for a period of up to nine months.

Equity Offering

On July 18, 2018, we 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 us of up to 5,175,000 shares of our 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 pursuant to 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, we closed the offering, including the full exercise of the underwriters' option to purchase 675,000 additional shares of common stock. We received net proceeds of approximately $92.1 million, after deducting $6.3 million relating to underwriting discounts and commissions and offering expenses.

Vifor Fresenius Medical Care Renal Pharma Ltd. License Agreement

On May 17, 2018, we entered into a license agreement, or the VFMCRP Agreement, with VFMCRP (see Item 1. Business – Commercial Partnerships and License Agreements).

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 chronic kidney disease associated pruritus 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)

CKD-aP (also known as uremic pruritus) can occur in patients with chronic kidney disease, or 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, or DOPPS, 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.

Other Causes of Pruritus

There are many other systemic diseases that can trigger pruritus in patients. They include cholestatic liver disease, endocrinologic disease (e.g. hyperthyroidism), malignancy (e.g. Hodgkin lymphoma), hematologic disease (e.g. polycythemia vera), atopic dermatitis, eczema, 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 – Pain and Post-Operative Nausea and Vomiting (PONV) Management

Pain is generally categorized by its duration as either acute or chronic, by its severity, as either mild, moderate or severe, and its type and/or causality, such as postoperative or neuropathic. Acute pain is typically caused by an injury resulting in nerve, tissue or bone damage and is expected to subside in severity when the injury heals. Postoperative pain is a subset of the acute pain market. According to the International Association for the Study of Pain, more than 46 million inpatient and 53 million outpatient surgeries are performed annually in the United States. PONV is another significant issue for many patients in the postoperative setting occurring in over 30% of patients.

Chronic pain, on the other hand, is prolonged, and can be the long-term result of an acute injury or an ongoing disease condition, such as neuropathic pain associated with diabetes. According to an Institute of Medicine report, chronic pain affects approximately 100 million U.S. adults, while millions of others experience acute pain caused by events such as surgery, injury, childbirth and illness. The most common causes of moderate-to-severe chronic pain are musculoskeletal problems and inflammatory conditions. Injuries from accidents resulting in fractures, dislocations or soft tissue injury, as well as lower back pain, are the most frequent causes of musculoskeletal pain. Although these injuries are mostly non-fatal, the cost in terms of long-term disability, medical expense and lost productivity is large.

Post-Operative Pain and Chronic Pain Markets

According to IQVIA, the total U.S. market for pain management pharmaceuticals was $45.3 billion in 2018. The prescription pain management market in the United States is still dominated by opioid analgesics, which, according to IQVIA data, represented 52% of the 368 million analgesic prescriptions written in 2018 and accounted for sales of $5.7 billion in that year. Opioid analgesics decrease the perception of pain by stimulating mu, delta and/or kappa opioid receptors. All of these receptors are involved in modulating pain signals. The most widely used opioid analgesics, including hydrocodone, oxycodone, morphine, and fentanyl, act primarily through the activation of mu opioid receptors in the CNS. However, because of the wide distribution of mu opioid receptors throughout the brain, morphine and other mu opioid analgesics also trigger a characteristic pattern of adverse “central” side effects, including nausea and vomiting, itching and respiratory depression. Mu opioids are also known to cause euphoria, which can lead

to misuse, abuse and addiction issues.

Moderate-to-severe chronic pain is typically treated with prescription products including immediate release and long-acting opioids, such as the branded products OxyContin® (oxycodone), NUCYNTA® ER (tapentadol) and Opana® ER (oxymorphone), and combination products that include an opioid combined with an NSAID or acetaminophen, such as the branded products Vicodin® (hydrocodone and acetaminophen) and Percocet® (oxycodone and acetaminophen). Prescription products for chronic pain are usually in oral tablet or capsule form because the vast majority of these patients are taking these medications outside of the hospital setting.

Despite the size of the pain management market, there has been little innovation in the development of new analgesics, with nearly all recent new drug approvals limited to reformulations and improved methods of delivery of existing therapeutics. Mu opioids continue to be the most prescribed drugs for pain management, despite their side effects and the potential for misuse, abuse and addiction. These concerns often cause healthcare providers to administer or prescribe less than optimal doses of mu opioids, or patients to take lower than prescribed doses, resulting in inadequate pain relief. Consequently, we believe that the pain market represents a therapeutic area with substantial unmet needs for patients in pain, for physicians who must balance pain control with risks of causing severe adverse events, and for healthcare organizations that bear the costs of managing the consequences of undertreated pain and drug-related adverse events. We believe that CR845/difelikefalin, with its novel mechanism of action, will likely be attractive to patients and physicians, as well as hospitals and payers, as a treatment for moderate-to-severe pain because of its ability to provide pain relief without opioid-related adverse events or abuse and addiction issues associated with currently approved mu opioid analgesics.

PONV Market

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, or HD, patients suffering from moderate to severe CKD-aP. In January 2019, we completed enrollment in this trial and expect top-line data to read out in the second quarter of 2019. In August 2018, we initiated a global Phase 3 study (KALM-2) with KORSUVA (CR845/difelikefalin) injection in HD 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 half of 2019. In addition, we also have a 52-week single arm safety study ongoing in the United States that has currently over 100 patients that have completed at least 6 months of treatment. These studies 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 HD 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. In March 2017, we reported positive Phase 2 data from a trial of KORSUVA (CR845/difelikefalin) injection in HD patients with CKD-aP where patients receiving KORSUVA (CR845/difelikefalin) experienced a highly statistically significant reduction in worst itch scores as well as statistically significant and clinically meaningful improvements

in quality of life measures versus placebo after eight weeks of treatment. KORSUVA (CR845/difelikefalin) was observed to be well tolerated, with no significant drug-related events. Earlier, in July 2015, we reported similar positive top-line safety and efficacy results from a smaller Phase 2 trial in HD patients with CKD-aP after two weeks of treatment.

Build a specialty sales and marketing organization to commercialize KORSUVA (CR845/ difelikefalin) injection for the treatment of CKD-aP in HD patients in the United States, if approved. If KORSUVA (CR845/ difelikefalin) injection is approved by the FDA for the treatment of CKD-aP in HD 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 HD 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 company 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 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 injection for the treatment of CKD-aP in the United States except in the dialysis clinics of Fresenius Medical Care North America (FMCNA), where we and VFMCRP will promote KORSUVA injection under a profit-sharing arrangement based on net FMCNA clinic sales recorded by us. In addition, we already have development and commercialization agreements with Maruishi and CKDP for development of KORSUVA (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, chronic liver disease associated pruritus, or CLD-aP, and certain dermatologic conditions. 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 for the treatment of pruritus in patients with stage III to V (moderate to severe) CKD as well as in patients with CLD-aP. In July 2018, we initiated a double blind, randomized, placebo-controlled Phase 2 study with Oral KORSUVA in stage III to V (moderate-to-severe) CKD patients with CKD-aP. The Oral KORSUVA doses selected in the Phase 2 study were based on drug exposure data from the Phase 1 safety and pharmacokinetic, or PK, study with Oral KORSUVA (CR845/difelikefalin) in patients with stage III to V (moderate-to-severe) CKD. We also conducted a Phase 1 safety/ tolerability and PK study in patients with CLD due to various underlying etiologies to support an efficacy proof-of-concept Phase 2 study in similar patients with CLD-aP. In addition, we also expect to initiate a Phase 2 trial in certain dermatologic conditions, including atopic dermatitis, with Oral KORSUVA around mid-year 2019.

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 expect to seek 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.

Establish partnerships for further development and commercialization of Oral CR845/difelikefalin for chronic pain indications. We do not intend to further develop and commercialize Oral CR845/difelikefalin for chronic pain indications on our own and will likely seek partnerships and collaborations with companies that have development and commercialization expertise in chronic pain. In June 2017, we announced top-line results of Oral CR845/difelikefalin from the Phase 2b double blind placebo-controlled trial where three different doses (1, 2.5 and 5 mg twice daily) of CR845/difelikefalin were evaluated in patients with moderate to severe osteoarthritis, or OA, of the hip or knee over an eight-week treatment period. While the study did not meet statistical significance in reduction in pain scores across all OA patients (OA of hip and knee), at the 5 mg twice daily dose, patients with OA of the hip experienced statistically significant reduction in mean weekly pain score.

Our Product Candidates

Our lead product candidate, CR845/difelikefalin, is a new chemical entity, which is designed to selectively stimulate kappa, rather than mu, and delta opioid receptors outside of the CNS. CR845/difelikefalin has been designed with specific chemical characteristics to restrict its entry into the CNS and further limit its mechanism of action to kappa opioid receptors in the peripheral nervous system and on immune cells. In addition to the side effects associated with activation of mu opioid receptors in the CNS, activation of kappa receptors in the CNS is also known to result in some undesirable effects, including dysphoria. CR845/difelikefalin is designed to specifically target kappa receptors located on peripheral nervous system and certain immune cells that results in modulation of pain signals as well as relief from pruritus or itch associated with certain chronic diseases. Since CR845/difelikefalin is designed to modulate 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 2,000 human subjects in Phase 1, Phase 2 and Phase 3 clinical trials as an I.V. infusion, rapid 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 disease as well as moderate-to-severe pain due to the following attributes:

- novel, peripherally-acting, kappa opioid receptor 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;
- 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 chronic pain or pruritus 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 Chronic Kidney Disease-Hemodialysis	• KALM-1 (U.S.) and KALM-2 (Global) Phase 3 efficacy trials ongoing. KALM-1: enrollment completed • Phase 3 long term safety trial ongoing • Phase 2 adaptive trial completed and data reported • 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 efficacy trial ongoing	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus Chronic Liver Disease (CLD)	• Phase 1 safety and PK trial completed; Phase 2 initiation expected in Q2 2019	Cara (Worldwide, other than South Korea); CKDP (South Korea)
Pain	CR845/difelikefalin Injection	Acute Post-Operative Pain	• Adaptive Phase 2/3 trial completed; Top-line data released	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral CR845/difelikefalin	Chronic Pain	• Phase 2b osteoarthritis, or OA, clinical trial completed. Top-line data released	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	CR701	Chronic Pain	• Preclinical	Cara (Worldwide)

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

Pruritus, or itch, is associated with certain chronic conditions such as kidney disease, atopic dermatitis, eczema, liver disease and psoriasis. Based on KORSUVA (CR845/difelikefalin)'s effect on the peripheral nervous system and immune cells which result in anti-pruritic and anti-inflammatory effects in non-clinical models, we believe KORSUVA (CR845/difelikefalin) has the potential to treat pruritus associated with multiple medical conditions.

CKD-associated pruritus, or CKD-aP, also known as uremic pruritus, is an intractable systemic itch condition with high prevalence in patients with CKD for which there are no approved therapeutics in the United States or Europe.

In the first quarter of 2018, we initiated the first pivotal Phase 3 efficacy trial of KORSUVA (CR845/difelikefalin) injection in the United States for the treatment of CKD-aP in patients undergoing hemodialysis. The enrollment in this study is now complete and we expect top-line data in the second quarter of 2019. In August 2018, we initiated a Global Phase 3 efficacy trial (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 addition to the efficacy trials, we are also conducting a 52-week Phase 3 safety study of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP.

In June 2017, the FDA granted breakthrough therapy designation for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe uremic 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). The primary efficacy endpoint is the proportion of patients 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. Secondary endpoints of the Phase 3 trial include assessment of itch-related quality of life changes measured using self-assessment 5-D Itch and Skindex-10 scales, as well as the proportion of patients achieving at least 4-point improvement from baseline in weekly mean of the daily 24-hour worst itching NRS score at week 12 and patient global impression of change. In January 2019, we announced the completion of enrollment in KALM-1 Phase 3 trial after a pre-specified interim conditional power analysis conducted by the Independent Data Monitoring Committee, or IDMC, that recommended no adjustment to the original trial size. Over 350 hemodialysis patients with CKD-aP have been randomized across approximately 60 clinical sites in the United States and we expect to report top-line data in the second quarter of 2019.

In August 2018, we announced the dosing of the first patient in the second Phase 3 efficacy trial (KALM-2) that is matching in design and size to the KALM-1 trial and will facilitate regulatory filings worldwide. This second Phase 3 trial is designed to enroll hemodialysis patients with moderate-to-severe pruritus in the United States as well as in multiple countries in Europe and Asia Pacific. Based on current enrollment projections, we expect to report top-line data from the KALM-2 trial in the second half of 2019.

Phase 3 Safety Trial of KORSUVA (CR845/Difelikefalin) Injection

In the second quarter of 2017, we initiated a 52-week Phase 3 safety trial that is expected to enroll up to 240 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 enrollment is nearing completion, with approximately 125 patients who have completed at least six months of treatment and approximately 40% of these patients have completed 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 September 2017.

Phase 2/3 Adaptive Design Trial of KORSUVA (CR845/Difelikefalin) Injection in Dialysis Patients

In June 2016, we initiated a two-part Phase 2/3 adaptive design trial of KORSUVA (CR845/difelikefalin) injection in dialysis patients suffering from moderate-to-severe uremic pruritus. In March 2017, we announced top-line data from

the Phase 2 trial, which was a randomized, double-blind, placebo-controlled trial of three doses of intravenous KORSUVA (CR845/difelikefalin) injection (0.5 mcg/kg, 1.0 mcg/kg and 1.5 mcg/kg) administered three times per week after dialysis over an eight-week treatment period in 174 patients with moderate-to-severe uremic pruritus.

The primary endpoint of this trial was the change from baseline of the mean worst itching score for week eight measured on a patient reported 24-hour worst itching intensity 11-point NRS scale. Patients receiving KORSUVA (CR845/difelikefalin) injection experienced a 68% greater reduction from baseline in worst itch scores than those receiving placebo ($p<0.0019$). The secondary endpoints of this trial focused on itch-related quality of life measures assessed using the Skindex-10 scale, 5-D itch scale, sleep disturbance subscale and others. In addition to reduction of pruritus, patients experienced substantial improvement in multiple itch-related quality of life (Skindex-10, 5-D Itch scale) measures and sleep over two months of treatment. Additionally, in a post-hoc analysis, (1) 64% of the patients treated at the 0.5 mcg/kg dose experienced at least a 3 point improvement from baseline with respect to the weekly mean NRS score versus 29% of patients on placebo ($p<0.01$), and (2) 51% of the patients treated at the 0.5 mcg/kg dose experienced at least a 4 point improvement from baseline with respect to the weekly mean NRS score versus 24% of patients on placebo ($p<0.05$).

Overall, KORSUVA (CR845/difelikefalin) was observed to be generally well tolerated over the eight-week treatment period and the unblinded Drug Safety Monitoring Board did not raise any safety concerns during the course of the trial. The most common treatment-emergent adverse events were somnolence, headache, dizziness, mental status changes, nausea and diarrhea, generally in line with what has been observed in previous clinical studies of KORSUVA (CR845/difelikefalin). The Phase 3 part of this study has been replaced by the KALM-1 Phase 3 trial.

Phase 2 Efficacy Trial in Dialysis Patients

In 2014, we conducted a Phase 2 randomized, double-blind, placebo-controlled proof-of-concept trial (Part B), which measured the efficacy of KORSUVA (CR845/difelikefalin) injection at the dose of 1.0 mcg/kg compared to placebo in reducing the intensity of itch in 65 dialysis patients with uremic pruritus over a two-week dosing period, who had baseline "worst itching" scores of greater than 40 mm on a visual analog scale, or VAS ranging from 0 to 100 mm. In July 2015, we reported positive top-line efficacy results from this trial, in which we observed that KORSUVA (CR845/difelikefalin) injection demonstrated statistically significant reduction in worst itch intensity as measured by VAS, the primary endpoint of the trial, as well as statistically significant improvement in quality of life measures such as Skindex-10, the trial’s secondary endpoint. The overall safety and tolerability profile was favorable. The dose of the Phase 2 study was informed by Phase 1 safety and pharmacokinetic, or PK, trial (Part A) that was conducted in subjects undergoing hemodialysis at doses ranging from 0.5 mcg/kg to 2.5 mcg/kg after each dialysis session up to three times per week.

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 dose levels (0.25 mg, 0.5 mg and 1 mg, once daily) of Oral KORSUVA versus placebo in approximately 240 stage III-V (moderate to severe) CKD patients with moderate-to-severe pruritus, with a pre-specified interim analysis 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 Itch Numeric Rating Scale, or 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 Itch NRS score at week 12. We expect top-line data from this trial in the second half of 2019.

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 trial was used to assess the PK and safety of different tablet strengths of Oral KORSUVA (CR845/difelikefalin) (for example, 0.25 mg, 0.5 mg and 1.0 mg), dosed daily over a one-week treatment period in three groups of patients with moderate renal impairment and three groups of patients with severe renal impairment (six groups total). The exposure levels achieved with Oral KORSUVA tablets were approximately equivalent to the exposure level achieved with 0.5 mcg/kg dose of I.V. KORSUVA 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.

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

Pruritus is a common and irritating symptom in patients with chronic liver disease, or 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 chronic liver disease, or CLD.

In the fourth quarter of 2017, we submitted an investigational new drug application, or IND, to the FDA for Oral KORSUVA (CR845/difelikefalin) for 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 (twice daily) in up to 60 patients with CLD and up to 12 matched healthy control subjects. Oral KORSUVA 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 was generally well tolerated with no unexpected safety signals reported. We expect to initiate a Phase 2 trial in chronic liver disease patients with moderate-to-severe pruritus in the second quarter of 2019.

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).

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- 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.

Phase 1 Safety and PK and Phase 2 Acute Pain Clinical Trials (Post-Surgery) of CR845/Difelikefalin Injection

Previously, in three different randomized, double-blind, placebo-controlled Phase 2 clinical trials, CR845/difelikefalin injection has been shown to be well tolerated and demonstrated efficacy of pain relief. Two of these trials were conducted in patients undergoing laparoscopic hysterectomy, a soft tissue surgical procedure, and a third trial was in patients undergoing bunionectomy, a hard tissue surgical procedure. Intravenous administration of CR845/difelikefalin resulted in statistically significant reductions in pain intensity, as measured by the sum of pain intensity difference. In addition, in both surgical models, CR845/difelikefalin injection exhibited an ability to decrease the opioid-related adverse events, or AEs, of nausea and vomiting associated with current therapies, along with no evidence of drug-related respiratory depression.

The safety profile of CR845/difelikefalin injection has been demonstrated in multiple studies. CR845/difelikefalin injection was observed to be generally well tolerated in all of these clinical trials. The most common treatment-emergent adverse events, or TEAEs, across evaluated populations in acute pain trials were transient facial tingling or numbness, dizziness and fatigue. In addition, a transient increase in urine output in the absence of electrolyte loss, otherwise known as aquaresis, was also observed, which in some subjects in acute pain trials was accompanied by asymptomatic elevations in plasma sodium that were generally considered to be clinically unimportant. No clinically significant changes in electrocardiogram characteristics have been observed in any of these studies. Importantly, there appeared to be no cases of dysphoria/hallucinations typically observed with prior-generation CNS-active kappa agonists.

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 IV 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 were the same. 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 acute pain or pruritus.

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 (>30 seconds duration) increase in $ETCO_2$ above baseline or to >50 mmHg, and a sustained reduction in SpO_2 to <92 percent.

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.

Oral CR845/Difelikefalin for Treatment of Osteoarthritis

We also investigated an oral version of CR845/difelikefalin, or Oral CR845/difelikefalin for pain relief, which we believe could be used to provide pain relief to patients with acute or chronic pain in an outpatient setting and also as an I.V.-to-oral transition, or step-down, therapy for hospital patients being prepared for discharge.

Phase 2b Trial of Oral CR845/Difelikefalin

In the third quarter of 2016 we initiated a Phase 2b trial with Oral CR845/difelikefalin, which was designed to evaluate three tablet strengths (1.0 mg, 2.5 mg and 5.0 mg), dosed twice-daily over an eight-week treatment period in 476 patients with OA of the knee or hip experiencing moderate-to-severe pain across the United States. The primary efficacy endpoint was the change from baseline at week eight, with respect to the weekly mean of the daily pain intensity score using an NRS score. Secondary endpoints included overall Patient Global Assessment, or PGA, score, and overall improvement in Western Ontario and McMaster Osteoarthritis Index, or WOMAC, scores, two commonly used patient-reported outcome measures, as well as mean reduction in rescue medication.

In June 2017, we announced top-line results from the Phase 2b trial. The results of the primary efficacy analysis of change from baseline in pain intensity NRS score comparing Oral CR845/difelikefalin (all doses) vs. placebo were not statistically significant across all patients (OA of the knee or hip). However, patients with OA of the hip maintained on the 5.0 mg dose to the end of the eight-week treatment period exhibited a statistically significant 39% reduction in mean joint pain score versus placebo ($p=0.043$); although this effect did not reach statistical significance in a combined analysis of all patients with OA of the knee or hip maintained on the 5.0 mg dose ($p=0.111$). For patients maintained on the 5.0 mg dose, there was a statistically significant increase in the proportion of patients whose OA pain was “very much improved” or “much improved” as indicated by PGA score in both the total patient group ($p <0.005$ vs. placebo) and in patients with primary OA of the hip ($p<0.006$ vs. placebo). The reduction in pain score in the 5.0 mg dose group in hip patients was accompanied by a reduction in mean rescue medication of 41% at week eight versus placebo. Patients maintained on the 1.0 mg and 2.5 mg tablet strengths did not exhibit significant reductions in mean joint pain scores compared to placebo. All tablet strengths were generally well tolerated with no drug-related serious adverse events. For the 5.0 mg dose, the most common adverse events reported at the >5 percent incidence

level were dry mouth (6%) and constipation (12%). There were no clinically significant changes in serum sodium levels observed during the eight-week treatment period for any dose group.

In 2015, we completed a Phase 2a trial of Oral CR845/difelikefalin in 80 patients with OA of the knee or hip with moderate-to-severe pain evaluating four tablet strengths (0.25 mg, 0.5 mg, 1.0 mg and 5.0 mg) administered twice a day over a two-week treatment period. We reported data that showed dose related reduction in mean joint pain score and that all four tablet strengths were observed to be generally well tolerated with no unexpected safety signals reported.

We do not intend to develop Oral CR845/difelikefalin in pain associated with OA on our own and will likely seek one or more potential partner(s) for further development of Oral CR845/difelikefalin in this indication.

CR701

In addition to our CR845/difelikefalin family of peripheral kappa agonists, we have discovered lead molecules that selectively modulate peripheral cannabinoid receptors. Studies on the effects of cannabis have led to the discovery of an endogenous system of ligands in humans involved in a number of physiological processes, including pain and inflammation. The main naturally occurring ligands for this system, anandamide and 2-arachidonoylglycerol (2-AG), activate a number of cannabinoid receptors, including CB1 and CB2 receptors. Like opioid receptors, CB1 and CB2 receptors are members of the G protein-coupled receptor superfamily. CB1 receptors and associated ligands are mainly localized in the brain, whereas CB2 receptors are found mainly in peripheral tissues, particularly immune cells such as leukocytes and mast cells, which have been shown to be involved in pain and inflammatory responses.

Our most advanced CB compound, CR701, is a peripherally-restricted, mixed-CB1/CB2 receptor agonist that selectively interacts with these cannabinoid receptor subtypes, with no off-target activities. The compound is orally bioavailable, active in preclinical models of inflammatory and neuropathic pain, and does not produce the side effects characteristic of centrally-active cannabinoids, such as sedation and hypothermia. Accordingly, CR701 would be expected to have substantially less abuse potential than centrally-active cannabinoids, but retain activity against therapeutically valuable peripheral targets, similar in principle to CR845/difelikefalin.

Commercial Partnerships 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 (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.

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 postoperative pain that suggests it would be well received by physicians, if approved. This research indicated that in addition to providing pain relief, reducing side effects such as nausea and vomiting, were among the highest unmet needs in the postoperative setting. In our three Phase 2 trials, I.V. CR845/difelikefalin demonstrated statistically significant pain relief and statistically significant reductions in nausea and vomiting. As a result, we believe that, if successful, I.V. CR845/difelikefalin is well positioned to address unmet needs in the postoperative pain 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 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. 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 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 the use 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 under certain circumstances the patent term may be extended for up to a further five (5) years 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, 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 sole remaining patent application claiming CR845/difelikefalin is still pending in Brazil. 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.

CR701

Our imidazoheterocycle cannabinoid compound patent portfolio, which is wholly owned by us, includes U.S. Patent Nos. 7,517,874; 8,431,565; and 8,859,538. These U.S. patents are due to expire no earlier than June 20, 2028. A related international PCT application was filed and sixteen national patent applications and a European regional patent application has been filed based on the international patent application. The European regional patent has been granted as have national patents in Australia, Canada, China, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Philippines, Singapore, Russia, South Africa and South Korea. These and any other patents resulting from the pending national patent applications, if issued, expire no earlier than June 20, 2028. A patent application claiming CR701 is still pending in Brazil.

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.

In addition, our kappa receptor opioid peptide international patent portfolio, which is wholly owned by us, includes claims to CR665, our first-generation kappa opioid receptor agonist, related compounds, and methods of using these compounds. The international PCT patent application PCT/US98/27282 was filed and progeny national patent applications have been granted in over 40 other countries. Granted patents with claims to CR665 were maintained in Brazil, Canada, China, France, Germany, India, Italy, Russia, Spain and the U.K. and expired on December 22, 2018, except for the Brazilian patent, the term of which has been extended to October 21, 2024 to compensate for patent office delays.

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 nalbuphine from Trevi Therapeutics, asimadoline from Tioga Pharmaceuticals, 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 – Acute Pain. We are developing I.V. CR845/difelikefalin for the management of acute postoperative pain in adult patients. The market for management of postoperative pain is highly fragmented and can be segmented into three general classes of products:

- mu opioid-based products, such as morphine, fentanyl, hydrocodone, and hydromorphone, all of which are available generically;
- local anesthetic-based products, such as lidocaine and bupivacaine, which are available generically; and
- adjunctive analgesics, which are defined as non-mu opioid pain-relieving drugs that provide additional control of postoperative pain.

There has been a trend in recent years for anesthesiologists to use all three classes of products to manage postoperative pain, often referred to as "multimodal analgesia." If approved, I.V. CR845/difelikefalin would be competing within the overall acute postoperative pain market, although we expect that it would compete primarily with injectable mu-opioid analgesics, such as morphine, fentanyl and hydromorphone. Although these products are generically available, they cause significant mu-opioid side effects such as nausea and vomiting, sedation, constipation and respiratory depression, which add significant cost to managing a post-operative patient.

In addition to the above products approved for use as adjunctive analgesics for moderate-to-severe pain, there have been clinical reports that generic drugs originally approved for other indications, such as gabapentin and pregabalin, as well as dexmedetomidine, dextromethorphan, and clonidine may exhibit efficacy in the treatment of postoperative pain, and these and other such drugs may be used off-label for this purpose and, therefore, also compete with I.V. CR845/difelikefalin. Additionally, numerous companies are developing additional product candidates for the treatment of acute postoperative pain.

Oral CR845/difelikefalin– Chronic Pain. The market for the management of moderate-to-severe chronic pain is highly fragmented and includes numerous generic as well as brand name products, including oral formulations of NSAIDs and controlled-release mu opioids. Common NSAIDs include Celebrex®, which is marketed by Pfizer, and naproxen and ibuprofen, which are available generically. Common branded oral mu opioids include, among others: Avinza®, an extended-release morphine sulfate capsule marketed by Pfizer; EXALGO®, an extended-release hydromorphone hydrochloride tablet marketed by Mallinckrodt; KADIAN®, an extended-release morphine sulfate capsule marketed by Allergan; NUCYNTA® ER, an extended release formulation of tapentadol marketed by Collegium and OxyContin®, a controlled-release oxycodone hydrochloride tablet marketed by Purdue Pharma. In addition to oral therapies, Janssen Pharmaceuticals markets Duragesic®, a fentanyl transdermal patch.

Because of the size of the chronic pain market and the substantial unmet need for products that are safe and effective, there are a large number of companies involved in the discovery, development, and/or marketing of such products. These product candidates include immediate release and extended release formulations of various NSAIDs and mu opioids. These include combination products that include mu opioid combined with an NSAID or acetaminophen, such as Abbvie's Vicodin® (hydrocodone and acetaminophen) and Endo Pharmaceuticals' Percocet® (oxycodone and acetaminophen). Additionally, there are other product candidates in development with non-opioid mechanisms of

action.

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.

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;
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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.

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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.

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 our other 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, 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.

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, individual 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 2019 contains additional drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. 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 already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. 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. 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.

Some of the provisions of the Health Care Reform Law have yet to be implemented, and there have been 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". On January 23, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Health Care Reform Law-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. 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 July 2018, CMS published a 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. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, 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 2027, unless additional congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers 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 March 5, 2019, we had 55 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 internet website is www.caratherapeutics.com. We make available free of charge on our website (under the heading “SEC Filings”) our Securities and Exchange, or SEC, filings, including our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Our website address is provided only as an inactive textual reference. The information provided on our website is not part of this Annual Report on Form 10-K and is not incorporated by reference herein. The SEC maintains an internet website (http://www.sec.gov) where our SEC filings may be accessed by the public.

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 $74.0 million, $58.1 million and $57.3 million for the years ended December 31, 2018, December 31, 2017 and December 31, 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $294.4 million. We expect to continue to incur significant expenses and operating and net losses over the next several years, as we continue to develop 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 collaborations with VFMCRP, Maruishi and CKDP, the receipt of payments under any future collaborations we may enter into, and our expenditures on other R&D activities.

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 atopic dermatitis;
- 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 products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We may never succeed in these activities and, even if we do, may never achieve profitability.

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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 developing our product candidates, including undertaking preclinical studies and conducting clinical trials of I.V. and Oral CR845/difelikefalin. We have not yet demonstrated an ability to obtain regulatory approval for, or successfully commercialize, a product candidate. In addition, as a relatively nascent business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown difficulties. 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 atopic dermatitis;
- 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 and our other future product candidates, 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, 2018, we will have sufficient funds to meet our projected operating requirements into 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 revenues in the near term is substantially 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 the first quarter of 2018, we initiated the first pivotal Phase 3 efficacy trial of KORSUVA (CR845/difelikefalin) injection in the United States for the treatment of CKD-aP in patients undergoing hemodialysis and, in January 2019, we announced the completion of enrollment for this trial. In August 2018, we initiated a Global Phase 3 efficacy trial of KORSUVA (CR845/difelikefalin) injection that is expected to enroll patients in the United States and multiple countries outside of the United States. In addition to the efficacy trials, we are also conducting a 52-week Phase 3 safety study of KORSUVA (CR845/difelikefalin) injection in hemodialysis patients with CKD-aP. In June 2018, we reported positive top-line data from our adaptive Phase 2/3 study of CR845/difelikefalin injection in patients undergoing abdominal surgery. The next steps for the acute post-operative pain and/or PONV program will be determined after we have completed detailed analysis of the data and consulted with the FDA. 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. We are also unable to give you any assurance regarding the next steps for our acute post-operative program after we review the completed detailed analysis of the data from our adaptive Phase 2/3 study of CR845/difelikefalin injection in patients undergoing abdominal surgery and consult with the FDA.

In addition to clinical development, KORSUVA (CR845/difelikefalin) injection will require regulatory approval, commercial manufacturing arrangements, 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 or any of our other 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, our product candidates, including KORSUVA (CR845/difelikefalin) injection, may not receive regulatory approval even if they are 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 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 atopic dermatitis. 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 Clinical Research Organizations, or 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. 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. 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 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 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.

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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.

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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.

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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 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.

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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, there are a large number of companies developing or marketing therapies for the treatment and management of postoperative acute pain, moderate to severe chronic pain and neuropathic pain, including many major pharmaceutical and biotechnology companies. Among the companies that currently market or are developing therapies that, if approved, our product candidates would potentially compete with include: Pfizer, Cumberland Pharmaceuticals, Horizon Pharmaceuticals, Mallinckrodt, Actavis, Purdue Pharma, Janssen Pharmaceuticals, Celgene, Endo Pharmaceuticals, Collegium, Pacira, Egalet, Collegium Pharmaceuticals and Pernix.

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 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 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 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 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 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 of our other product candidates 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 of our other 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 of our other product candidates, 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 of our other product candidates 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.

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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 do not yet have agreements established regarding commercial supply of our product candidates and may not be able to establish or maintain commercial manufacturing arrangements on commercially reasonable terms for KORSUVA (CR845/difelikefalin) injection, if approved, or any of our other product candidates, for which we obtain

approval in the future. 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 of our 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.

We currently only have one contract manufacturer for each of I.V. CR845 and Oral CR845 for use in our current clinical trials. However, we are also working with other manufacturers to develop additional formulations of Oral CR845 for use in the future. In addition, we do not have any long-term commitments from our suppliers of clinical trial material or guaranteed prices for our product candidates. 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 the long-term use of any such proprietary technology may lead to delays or interruptions in the regulatory approval or commercialization process, as well as increased costs. For example, we have developed a formulation of Oral CR845 based on proprietary technology of Enteris. Under our agreement with Enteris, it is providing to us clinical supplies for an oral tablet formulation of CR845 on a fee for service basis. Under the agreed scope of work for this agreement, Enteris is using its proprietary formulation technology for oral delivery of peptides to provide a tablet formulation of CR845 with suitable characteristics to use in clinical testing. We have not yet negotiated terms related to our use of such technology for commercial manufacturing of Oral CR845 and we may not be able to do so on commercially reasonable terms, or at all. If we fail to enter into an agreement to use such proprietary technology, we may be forced to reformulate Oral CR845 which could result in significantly delaying commercializing Oral CR845 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, and our other product candidates, 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 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 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 and civil monetary penalties law, including, without limitation, the federal civil False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, 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 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. 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, individual 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 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 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.

In November, 2018, CMS finalized the End-Stage Renal Disease Prospective Payment System, or ESRD PPS, rule for the calendar year 2019. In the ruling, CMS expands the Transitional Drug Add-on Payment Adjustment, or TDAPA, to all new renal dialysis drugs and biological products to be reimbursed at Average Selling Price, or ASP, for a period of two years. The changes to the drug designation policy and TDAPA payment will be effective January 1, 2020. 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 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.

Some of the provisions of the Health Care Reform Law have yet to be implemented, and there have been 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". On January 23, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Health Care Reform Law-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. 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 July 2018, CMS published a 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. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, 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 2027, unless additional congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers 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 2019 contains additional drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. 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 already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, in October 2018, CMS proposed a new

rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product, and on January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. 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 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 prosecuted 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. 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 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 product candidates may infringe. There could also be existing patents of which we are not aware that KORSUVA (CR845/difelikefalin) injection or our other 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 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 our other product candidates are 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.

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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 March 5, 2019, we had 55 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. However, while we remain an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. When we cease to be an emerging growth company next year, we will be required to incur substantial additional professional fees and internal costs to expand our accounting and finance functions in order to include such attestation report.

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. Our internal control over financial reporting will not prevent or detect all error and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system’s objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected. If we identify one or more material weaknesses in our internal controls, 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.

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 March 5, 2019, 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 product candidates;
- the commercial success of KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or our other product candidates, if approved by the FDA;
- results of clinical trials of KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or our other product candidates 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 product candidates, which would likely further delay any such approval;
- if KORSUVA (CR845/difelikefalin) injection or any of our other 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 and enter into third party manufacturing arrangements capable of manufacturing KORSUVA (CR845/difelikefalin) injection or our other 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), our other product candidates, or the product candidates of our competitors; and
- if KORSUVA (CR845/difelikefalin) injection, Oral KORSUVA (CR845/difelikefalin) or other 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.

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

We are an emerging growth company and we are taking advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We will remain an emerging growth company until December 31, 2019.

Even following the termination of our status as an emerging growth company, we will be able to take advantage of the reduced disclosure requirements applicable to smaller reporting companies (as that term is defined in Rule 12b-2 of the Exchange Act) and, in particular, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. To the extent that we are no longer eligible to use exemptions from various reporting requirements, we may be unable to realize our anticipated cost savings from these exemptions, which could have a material adverse impact on our operating results.

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

Our net operating loss, or NOL, carryforwards and research and development, or R&D, tax credits may expire and not be used. As of December 31, 2018, we had federal and state NOL carryforwards of approximately $274.8 million and $268.0 million, respectively, and we also had federal and state R&D tax credit carryforwards of approximately $9.9 million and $1.2 million, respectively. Our NOL carryforwards will begin expiring in 2026 for federal purposes 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 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 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 and 2018, together with private placements and other transactions that have occurred, may have triggered such an ownership change. 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 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, continued suspension of 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 settlement 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 March 5, 2019, there were 33 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 January 31, 2014 (the first day our stock was traded on the Nasdaq Global Market) 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

	1/31/2014	12/31/2014	12/31/2015	12/31/2016	12/31/2017	12/31/2018
Cara Therapeutics, Inc.	100	77.23	130.60	71.96	94.81	100.70
NASDAQ Biotechnology	100	123.71	137.83	107.94	130.67	118.48
NASDAQ Composite	100	115.40	122.02	131.17	168.22	161.68

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 of 1933, as amended, 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, 2018, 2017 and 2016 and as of December 31, 2018 and 2017 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, 2015 and 2014 and as of December 31, 2016, 2015 and 2014 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,				
	2018	2017	2016	2015	2014
	(in thousands, except share and per share data)				
Statement of Operations Data:					
Revenue:					
License and milestone fee revenue	$13,436	$530	$—	$1,710	$302
Collaborative revenue	—	313	—	2,093	2,201
Clinical compound revenue	33	68	86	—	674
Total revenue (1)	13,469	911	86	3,803	3,177
Operating expenses:					
Research and development	75,531	48,524	49,253	21,221	15,068
General and administrative	15,320	11,872	9,233	7,770	6,181
Total operating expenses	90,851	60,396	58,486	28,991	21,249
Operating loss	(77,382)	(59,485)	(58,400)	(25,188)	(18,072)
Other income	2,980	1,156	652	101	126
Loss before benefit from income taxes	(74,402)	(58,329)	(57,748)	(25,087)	(17,946)
Benefit from income taxes	389	204	468	397	201
Net loss	$(74,013)	$(58,125)	$(57,280)	$(24,690)	$(17,745)
Net loss per share:					
Basic and Diluted	$(2.06)	$(1.86)	$(2.10)	$(1.00)	$(0.85)
Weighted average shares:					
Basic and Diluted	35,892,786	31,202,842	27,279,008	24,620,372	20,965,935

	As of December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
Balance Sheet Data:					
Cash and cash equivalents and marketable securities (2)	$182,779	$92,569	$58,276	$106,740	$52,663
Total assets	190,823	97,004	63,828	110,897	55,934
Deferred revenue (3)	42,009	—	—	—	1,452
Total liabilities	57,193	10,224	13,103	5,853	4,272
Total stockholders' equity	133,630	86,780	50,725	105,044	51,662

(1) The changes in revenue for the years ended December 31, 2014 to December 31, 2015 and December 31, 2017 to December 31, 2018 reflect upfront payments in connection with continuing our collaborative work with Maruishi in 2014 and 2015, milestone payments earned under our collaborations with Maruishi in 2014 and 2015 and with 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 (refer to the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations — Collaborations and License Agreements with VFMCRP, Maruishi and CKDP, Results of Operations” and Note 11 of Notes to Financial Statements, Collaboration and License Agreements, in this Annual Report on Form 10-K).

(2) The increases in cash and cash equivalents and marketable securities from December 31, 2017 to December 31, 2018, December 31, 2016 to December 31, 2017 and from December 31, 2014 to December 31, 2015 reflects the proceeds from our follow-on offering of our common stock in July 2018, 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 (refer to Note 9 of Notes to Financial Statements, Stockholders' Equity, in this Annual Report on Form 10-K).

(3) The increase in deferred revenue from December 31, 2017 to December 31, 2018 was due to the upfront payment from VFMCRP related to the license agreement entered into in May 2018 (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 with a primary focus on pruritus as well as pain by selectively targeting peripheral kappa opioid receptors. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), a first-in-class kappa opioid receptor agonist that targets the body's peripheral nervous system, as well as certain immune cells.

In 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, and is currently being investigated in Phase 3 trials in hemodialysis patients with CKD-aP. We have partnered with Vifor Fresenius Medical Care Renal Pharma Ltd., or 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 Pharmaceutical Co. Ltd., or Kissei), and South Korea (collaboration agreement with 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 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 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.

Recent Developments

Chief Medical Officer

Effective October 22, 2018, we appointed Joana Goncalves, M.D., as our new Chief Medical Officer, or CMO. Prior to joining us, Dr. Goncalves was the Vice President, Global Medical Affairs for Dermatology and Neurology at Celgene Corporation. Previously, she held various positions at LEO Pharma Inc., the U.S. subsidiary of Leo Pharma A/S and at Novartis Pharmaceuticals. Dr. Goncalves received her M.D. from The University of Cape Town, South Africa. On October 22, 2018, we entered into a Separation and Consulting Agreement with Joseph Stauffer, D.O., our former CMO, pursuant to which he will provide consulting services to us for a period of up to nine months.

Equity Offering

On July 18, 2018, we 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 us of up to 5,175,000 shares of our 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 pursuant to 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, we closed the offering, including the full exercise of the underwriters' option to purchase 675,000 additional shares of common stock. We received net proceeds of approximately $92.1 million, after deducting $6.3 million relating to underwriting discounts and commissions and offering expenses.

VFMCRP License Agreement

On May 17, 2018, we entered into a license agreement with VFMCRP (see Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations – Collaboration and License Agreements).

Collaboration and License Agreements

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 the U.S. except in the dialysis clinics of Fresenius Medical Care North America (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.

In April 2013, we entered into a license agreement, or the Maruishi Agreement, with Maruishi Pharmaceutical Co., Ltd., or 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.

In April 2012, we entered into a license agreement, or the CKDP Agreement with Chong Kun Dang Pharmaceutical Corporation, or 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.

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 $5.2 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 2019 will increase over those for 2018. 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 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.

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We anticipate that our general and administrative expenses for 2019 will generally approximate those for 2018 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 and realized gains and losses on the sale of marketable securities and property and equipment.

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, 2018, 2017 and 2016

Revenue

	Year Ended December 31,						
	2018			2017			2016
	Dollar amounts in thousands						
		% change			% change		
License and milestone fees revenue	$13,436	2436	%	$530	100	%	$ —
Collaborative revenue	—	-100	%	313	100	%	—
Clinical compound revenue	33	-51	%	68	-21	%	86
Total revenue	$13,469	1379	%	$911	959	%	$ 86

License and milestone fee revenue

License and milestone fee revenue of $13.4 million for the year ended December 31, 2018 was related to license fees earned by us during the period 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. There was no license and milestone fee revenue for the year ended December 31, 2016 (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, 2018 and 2016. 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 $33, $68 and $86 for the years ended December 31, 2018, 2017 and 2016, respectively, related to the sale of clinical compound to Maruishi.

Research and Development Expense

	Year Ended December 31,					
	2018		2017			2016
	Dollar amounts in thousands					
		% change			% change	
Direct clinical trial costs	$56,625	66	%	$34,075	-9	% $37,257
Consultant services in support of clinical trials	3,406	74	%	1,959	5	% 1,860
Stock-based compensation	4,395	81	%	2,433	87	% 1,301
Depreciation and amortization	288	-31	%	418	-50	% 839
Other R&D operating expenses	10,817	12	%	9,639	21	% 7,996
Total R&D expense	$75,531	56	%	$48,524	-1	% $49,253

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 I.V. KORSUVA (CR845/difelikefalin) in CKD patients undergoing hemodialysis, the Phase 3 long-term safety study of I.V. KORSUVA (CR845/difelikefalin) 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 I.V. KORSUVA (CR845/difelikefalin) 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.

For the year ended December 31, 2017 compared to the year ended December 31, 2016, the net decrease in direct clinical trial costs and related consultant costs primarily resulted from decreases totaling $7.0 million, mainly from the Phase 2b clinical trial of Oral CR845/difelikefalin in OA patients and the Phase 2/3 I.V. KORSUVA (CR845/difelikefalin) clinical trial in patients with uremic pruritus, a decrease of $4.5 million of CR845/difelikefalin drug manufacturing costs and a decrease of $3.7 million for the cost of toxicology studies. Those costs were partially offset by an increase of $12.1 million, mainly from the Phase 2/3 I.V. CR845/difelikefalin adaptive pivotal clinical trial in postoperative pain, the Phase 1 safety and pharmacokinetic trial of multiple doses of Oral KORSUVA (CR845/difelikefalin) in CKD patients undergoing hemodialysis, the 52-week Phase 3 safety study of I.V. KORSUVA (CR845/difelikefalin) in hemodialysis patients with uremic pruritus, and start-up costs associated with the 12-week Phase 3 study of I.V. KORSUVA (CR845/difelikefalin) in CKD patients undergoing hemodialysis. The increase in

stock-based compensation expense relates primarily to an increase in the number of options outstanding as a result of increased employee headcount and stock option awards granted to non-employee consultants, which are marked to market each quarter, and resulted from an increase in the market price of our common stock. The decrease in depreciation and amortization expense primarily reflects the acceleration of amortization of the leasehold improvements at our Shelton, Connecticut facility related to research and development activities prior to the relocation of our corporate headquarters to Stamford, Connecticut in May 2016 (see Note 17 of Notes to Financial Statements, Commitments and Contingencies, in this Annual Report on Form 10-K). The increase in other R&D operating expenses was primarily the result of an increase in personnel-related costs, partially offset by a decrease in rent expense, primarily due to the recognition in 2016 of all of the remaining rent expense allocable to research and development activities due during the remaining term of the Shelton operating lease.

The following table summarizes our R&D expenses by product candidate for the years ended December 31, 2018, 2017 and 2016:

	Year Ended December 31,					
	2018		2017			2016
	Dollar amounts in thousands					
		% change			% change	
External research and development expenses:						
I.V. CR845 - Pruritus	$35,781	373	%	$7,566	-31	%	$11,042
I.V. CR845 - Pain	6,386	-52	%	13,226	8	%	12,202
Oral CR845 - Pruritus	15,670	138	%	6,594	28	%	5,139
Oral CR845 - Pain	2,194	-75	%	8,648	-19	%	10,734
Internal research and development expenses	15,500	24	%	12,490	23	%	10,136
Total research and development expenses	$75,531	56	%	$48,524	-1	%	$49,253

General and Administrative Expense

	Year Ended December 31,					
	2018		2017			2016
	Dollar amounts in thousands					
		% change			% change	
Professional fees and public/investor relations	$2,906	29	%	$2,252	11	%	$2,032
Stock-based compensation	5,700	46	%	3,897	160	%	1,499
Depreciation and amortization	82	6	%	77	-88	%	626
Other G&A operating expenses	6,632	17	%	5,646	11	%	5,076
Total G&A expense	$15,320	29	%	$11,872	29	%	$9,233

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.

For the year ended December 31, 2017 compared to the year ended December 31, 2016, the increase in professional fees and public/investor relations was due primarily to an increase in public/investor relations costs. The increase in stock-based compensation primarily resulted from increased employee headcount, including our current Chief Financial Officer, the acceleration of vesting of outstanding stock option awards upon the retirement of our former Chief Financial Officer, and stock option awards granted to non-employee consultants, which are marked to market each quarter, and resulted from an increase in the market price of our common stock. The decrease in depreciation and amortization expense reflects the acceleration of amortization of our leasehold improvements at our Shelton,

Connecticut facility related to general and administrative activities prior to the relocation of our corporate headquarters in May 2016. The increase in other G&A operating expenses was primarily the result of an increase in personnel-related costs, partially offset by a decrease in rent expense, primarily due to the recognition in 2016 of all of the remaining rent expense allocable to general and administrative activities due during the remaining term of the Shelton operating lease.

Other Income

	Year Ended December 31,								
	2018			2017			2016		
	Dollar amounts in thousands								
		% change			% change				
Other income	$2,980	158	%	$1,156	77	%	$652		

During 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.

For the year ended December 31, 2017 compared to the year ended December 31, 2016, the increase in other income was primarily due to an increase in dividend and interest income resulting from higher interest rates on a higher average balance of our portfolio of investments in the 2017 period.

Benefit from Income Taxes

For the years ended December 31, 2018, 2017 and 2016, pre-tax losses were $74.4 million, $58.3 million and $57.7 million, respectively, and we recognized a benefit from income taxes of $389 thousand, $204 thousand and $468 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, 2018, 2017 and 2016.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception and through December 31, 2018, we have raised an aggregate of approximately $486.6 million to fund our operations, including (1) net proceeds of $309.8 million from the sale of shares of our common stock in four 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 $88.9 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 future operations, including our planned clinical trials, we filed a shelf registration statement on Form S-3 (File No. 333-216657), which the Securities and Exchange Commission, or SEC, declared effective on March 24, 2017. The shelf registration statement provides for aggregate offerings of up to $250 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 shelf registration statement (File No. 333-203072) that was declared effective on May 13, 2015.

On April 5, 2017, we completed a public offering of 5,117,500 shares of our common stock, including 667,500 shares sold upon the full exercise by the underwriters of their option to buy additional shares pursuant to our shelf registration statement. We received net proceeds of $86.2 million after deducting the underwriting discounts and commissions and offering expenses paid by us. The proceeds of the offering are/were being used to fund our clinical and research development activities, including the ongoing Phase 3 program for I.V. KORSUVA (CR845/difelikefalin) in CKD-aP or uremic pruritus, additional trials of Oral CR845/difelikefalin in other diseases associated with pruritus, the recently completed Phase 2/3 I.V. CR845/difelikefalin adaptive clinical trial in

postoperative pain, as well as for working capital and general corporate purposes.

On July 18, 2018, we 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 us of up to 5,175,000 shares of our 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 by pursuant to our 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 a prospectus supplement dated July 18, 2018, which was filed with the SEC on July 20, 2018.

On July 23, 2018, we closed the offering, including the full exercise of the underwriters' option to purchase 675,000 additional shares of common stock. We received net proceeds of approximately $92.1 million, after deducting $6.3 million relating to underwriting discounts and commissions and offering expenses.

We intend to use the net proceeds from this most recent underwritten offering to fund our clinical and research development activities, including the completion of our Phase 3 programs and submission of a new drug application to the FDA for KORSUVA (CR845/difelikefalin) injection for the treatment of CKD-aP in hemodialysis patients, the advancement of Oral KORSUVA (CR845/difelikefalin) into Phase 2 trials for the treatment of CKD-aP in Stage III-V patients and CLD patients, the expansion of our Oral KORSUVA program into certain dermatologic conditions and the exploration of further development of CR845/difelikefalin injection in the post-operative setting after consultation with the FDA, as well as for working capital and other general corporate purposes.

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. We believe that the use of a shelf registration statement provides us with the flexibility to raise additional capital to finance our operations as needed.

As of December 31, 2018, we had $182.8 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 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.

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, 2018, we have received milestone payments of $2.5 million before contractual foreign currency exchange adjustments.

During the first quarter of 2017, Maruishi entered into a sub-license agreement with another Japanese pharmaceutical company for the development and sales/marketing of CR845/difelikefalin in patients with uremic pruritus in Japan, as a result of which we received a payment of $843 thousand.

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, 2018, we have received milestone payments of $1.5 million before South Korean withholding tax.

The next potential milestone that could result in us receiving payment under the CKDP Agreement will be for a clinical development milestone for the completion by us in the United States of a Phase 3 trial of CR845/difelikefalin in uremic pruritus. If achieved, this milestone will result in a payment of $750 thousand, before South Korean withholding tax, being due to us.

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 $74.0 million, $58.1 million and $57.3 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $294.4 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;
- 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 an NDA submission, and conducting Phase 1 and Phase 2 trials of Oral (CR845/difelikefalin) in patients with CKD-aP, CLD-aP and certain dermatologic conditions, we expect that our existing cash and cash equivalents and available-for-sale marketable securities as of December 31, 2018 will be sufficient for us to fund our currently anticipated operating expenses and capital expenditures into 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 Tax Cuts and Jobs Act of 2017, or the Act, 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 Act, 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.

In addition, net operating losses, or 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.

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, 2018, 2017 and 2016:

	Year Ended December 31,		
	2018	2017	2016
	Amounts in thousands		
Net cash used in operating activities	$(22,301)	$(54,827)	$(47,381)
Net cash (used in) provided by investing activities	(82,819)	(36,500)	45,018
Net cash provided by financing activities	110,813	87,923	123
Net increase (decrease) in cash, cash equivalents and restricted cash	$5,693	$(3,404)	$(2,240)

Net cash used in operating activities

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 (which includes $1.7 million related to the vesting of restricted stock units), 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 operating activities for the year ended December 31, 2016 consisted primarily of a net loss of $57.3 million, a $6.0 million inflow from net changes in operating assets and liabilities and a $3.9 million cash inflow from net non-cash charges. The net change in operating assets and liabilities primarily consisted of cash inflows of $6.3 million from an increase in accounts payable and accrued expenses and $0.2 million from a decrease in prepaid expense, primarily related to a decrease in prepaid clinical costs. Those cash inflows were partially offset by cash outflows of $0.5 million due to an increase in income tax receivable from the State of Connecticut under the Connecticut R&D Tax Credit Exchange Program. Net non-cash charges primarily consisted of depreciation and amortization expense of $1.5 million and stock-based compensation expense of $2.8 million, partially offset by deferred rent costs of $0.1 million and accretion/amortization on available-for-sale marketable securities of $0.2 million.

Net cash (used in) provided by investing activities

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 investing activities for the year ended December 31, 2016, primarily included cash inflows of $80.4 million from maturities of available-for-sale marketable securities and $34.0 million from the sale of available-for-sale marketable securities. Those cash inflows were partially offset by cash outflows of $68.6 million from the purchase of available-for-sale marketable securities and $0.7 million of cash paid for purchase of property and equipment.

Net cash provided by financing activities

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.

Net cash provided by financing activities for the year ended December 31, 2016 consisted primarily of proceeds of $123 thousand received from the exercise of stock options.

Contractual Obligations

The following table summarizes our significant contractual obligations as of December 31, 2018 (in thousands):

	Payment Due for the Year Ending December 31,					
	2019	2020	2021	2022	2023	Total
Stamford operating lease	$1,215	$1,240	$1,264	$1,288	$1,164	$6,171

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

We have no material non-cancelable purchase commitments with contract manufacturers or service providers, as we have generally contracted on a cancelable purchase order basis.

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.

Using this model, fair value is calculated based on assumptions with respect to (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.

Our 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 our stock price to below the exercise prices of awards, blackout periods during which exercises are not allowed, among others. Therefore, we believe that as of December 31, 2018, we do not have sufficient company-specific information available to determine the expected term based on our historical data. As a result, the expected term of stock options granted to employees and members of our Board of Directors is determined using the average of the vesting period and term (6.25 years), an accepted method for our option grants under the SEC's Staff Accounting Bulletin No. 110, Share-Based Payment.

Similarly, because we do not have sufficient company-specific information available to calculate the volatility of our common stock during the periods of the expected term of stock option grants (as noted above), expected volatility is based on an analysis of guideline companies in accordance with ASC 718. Volatility calculated in this manner has been in the range of 83% - 93% and 75% - 85% during the years ended December 31, 2018 and 2017, respectively. The actual volatility of our common stock from January 31, 2014 to December 31, 2018 and 2017 was 75% and 79%, respectively. A higher volatility input to the Black-Scholes option valuation model increases the resulting compensation expense, while a shorter expected term would result in a lower compensation expense.

The expected dividend yield is zero as we have never paid dividends and do 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. 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.

On the grant date of each stock option award prior to January 1, 2017, we applied a forfeiture rate in order to accrue share-based compensation expense based on an estimate of the number of stock options that are expected to vest. Estimated forfeiture rates were based upon historical data of awards that were cancelled prior to vesting. We adjusted the total amount of compensation cost recognized for each award, in the period in which each award vested, to reflect the actual forfeitures related to that award. To the extent that the actual forfeiture rate for an award was lower than the estimated forfeiture rate, additional compensation expense was recorded in the period that the award vested. Changes in our estimated forfeiture rate resulted in changes in the rate at which compensation cost for an award was recognized over its vesting period. As of January 1, 2017, we adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting, or ASU 2016-09. On the date of adoption of ASU 2016-09, we 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, we recorded a cumulative effect adjustment to stockholders' equity of $45 thousand for all stock option awards that were unvested as of that date.

We account for stock options issued to non-employee consultants under ASC 505, Equity-Based Payments to Non-Employees. As such, we estimate the fair value of each such option 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, and then revalue the stock option on each reporting date until performance is complete. Under ASC 505-50, upon re-measurement of each award, income or expense is recognized during its vesting term.

On January 1, 2019, we will adopt ASU No. 2018-07, Compensation – Stock Compensation (Topic 718), Improvements to Non-employee Share-Based Payment Accounting, or ASU 2018-07, which expands 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 will be remeasured through a cumulative-effect adjustment to equity (see Note 2 of Notes to Financial Statements, Summary of Significant Accounting Policies, in this Annual Report on Form 10-K).

The assumptions 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.

Marketable Securities

We invest our excess cash in various types of securities, including money market funds, corporate bonds, commercial paper, municipal bonds and obligations of the U.S. government and U.S. government-sponsored entities. We deem certain of those investments to be marketable securities if the investment, or in the case of money market funds, the securities underlying the money market fund, meets the definition of a debt security in ASC section 320-10-20. We consider our marketable securities to be available-for-sale and, accordingly, these investments are recorded at fair value with unrealized gains and losses generally recorded in Accumulated other comprehensive income (loss) as a separate component of stockholders' equity. All available-for-sale marketable securities are reported in Marketable securities in the Balance Sheets.

We review each of our available-for-sale marketable securities for other-than-temporary impairment declines in fair value below its amortized 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 we will more likely than not be required to sell, the security before recovery of its amortized cost basis. Our 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 our investment portfolio is deemed to be other-than-temporary, we write down the security to its current fair value. If we intend to sell the security or it is more likely than not that we 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 (Loss), net of taxes. Credit losses are identified where we do not expect to receive cash flows sufficient to recover the amortized cost basis of a security.

Fair Value of Financial Instruments

We apply 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. We define 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, we consider 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.

Our 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 and cash equivalents, restricted cash, accounts payable and accrued liabilities approximate their carrying values due to the short-term nature of these financial instruments. Marketable securities are reported at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by pricing services, as described below.

In accordance with the accounting standard for fair value measurements, we have classified our financial instruments as level 1 or level 2 within the fair value hierarchy that is intended to increase consistency and comparability in fair value measurements and related disclosures. Fair values determined by Level 1 inputs utilize quoted prices in active markets for identical assets and liabilities. Fair values determined by Level 2 inputs use 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. We did not have any financial instruments classified as Level 3 during the years ended December 31, 2018, 2017 or 2016.

We estimate the fair values of our financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, municipal bonds and commercial paper 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. We obtain a single price for each financial instrument and do not adjust the prices obtained from the pricing service.

We validate the prices provided by our 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 pricing service. After completing our validation procedures, we did not adjust or override any fair value measurements provided by our pricing services as of December 31, 2018 or 2017. While we believe that the valuation methodologies are appropriate, the use of valuation methodologies is highly judgmental and changes in methodologies can have a material impact on our results of operations.

R&D Expenses

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 CROs and other consultants, stock-based compensation for R&D employees and consultants and other outside expenses. Some expenses are based on estimates regarding the percentage of completion of a project. 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.

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 money market funds and 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, 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. As of December 31, 2017, we have invested $83.2 million of our cash reserves in such marketable securities. Those marketable securities include $43.2 million of investment grade debt instruments with a yield of approximately 1.70% and maturities through July 2018 and $40.0 million of money market funds with an average annual return of 1.32%.

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, 2018 and 2017, 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.

The information required by this Item 8 of Part II is incorporated by reference to the Financial Statements filed with this Annual Report on Form 10-K. See Item 15. Exhibits, Financial Statement Schedules in this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, 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, 2018. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2018, 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(e) and 15d-15(e) 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, 2018. Based on the assessment, management has concluded that, as of December 31, 2018, our internal control over financial reporting was effective.

This Annual Report on Form 10-K does not include an audit or attestation report from our registered public accounting firm regarding our internal control over financial reporting. Our management's report was not subject to audit or attestation by our registered public accounting firm pursuant to rules of the SEC that permit us to provide only management's report in this annual report for so long as we remain an "emerging growth company" under the Jumpstart Our Business Startups Act.

Changes in Internal Control Over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(f) and 15d-15(f) of the Exchange Act that occurred during the quarter ended December 31, 2018 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 Chief 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 following table sets forth information concerning our executive officers as of March 1, 2019.

Name	Age	Position(s)
Derek Chalmers, Ph.D., D.Sc.	54	President, Chief Executive Officer and Director
Mani Mohindru, Ph.D.	47	Chief Financial Officer and Chief Strategy Officer
Frédérique Menzaghi, Ph.D.	52	Chief Scientific Officer and Senior Vice President, R&D
Joana Goncalves, M.D.	45	Chief Medical Officer
Scott Terrillion	56	General Counsel, Secretary and Chief Compliance Officer

Derek Chalmers, Ph.D., D.Sc. Dr. Chalmers, one of our founders, has served as our President and Chief Executive Officer since September 2004 and has served as a member of our Board of Directors since July 2004. Dr. Chalmers has over 25 years' experience in the biotechnology industry with increasing levels of corporate and business responsibilities. Prior to founding Cara, Dr. Chalmers co-founded Arena Pharmaceuticals, Inc. (Nasdaq: ARNA), a drug discovery and development company, and served as its Vice President and Executive Director from June 1997 until May 2004. Dr. Chalmers holds a D.Sc. and Ph.D. in Pharmacology from the University of Glasgow.
Dr. Chalmers' qualifications to sit on our Board of Directors include his leadership, executive, managerial and business experience, historical knowledge of our company and his background and experience in the biotechnology industry, including having been a founder of a prior biotechnology company.

Mani Mohindru, Ph.D. Dr. Mohindru has served as our Chief Financial Officer and Chief Strategy Officer since August 2017. Prior to joining Cara, Dr. Mohindru served as Senior Vice President and Chief Strategy Officer at Curis, Inc., a biotechnology company, from March 2016 to July 2017. From April 2015 to February 2016, Dr. Mohindru served as Senior Vice President of Corporate Strategy and Investor Relations and from June 2013 to March 2015, Dr. Mohindru served as Vice President of Corporate Strategy and Investor Relations, each at Curis, Inc. From October 2012 to March 2016, Dr. Mohindru was the co-founder of ImmTox, Inc., a biotechnology company. From June 2011 to September 2012, Dr. Mohindru was a Senior Biotechnology Analyst at ThinkEquity, LLC, a research and investment banking firm. Previously, from June 2009 to May 2011, Dr. Mohindru was a Partner at Axon Healthcare Company, a strategic pharmaceutical and biotechnology consultancy firm that she co-founded. Dr. Mohindru was also a Managing Director at Capstone Investments in its investment banking division, a Vice President at Credit Suisse, and an Associate Research Analyst at global financial services firm, UBS. Dr. Mohindru completed her Ph.D. in Neurosciences at Northwestern University and she received both her B.S. in Human Biology and Masters in Biotechnology from the All India Institute of Medical Sciences, New Delhi, India.

Frédérique Menzaghi, Ph.D. Dr. Menzaghi, one of our founders, has led our preclinical research and pruritic clinical program since 2004. Since 2017, she has served as our Senior Vice President, Research and Development and was promoted to Chief Scientific Officer on March 6, 2019. Dr. Menzaghi has over 25 years of drug development and management experience in biotechnology in the field of ion channels and G protein-coupled receptors. Her expertise ranges from exploratory non-clinical research through clinical development. From 2003 to 2004, she served as Vice

President, Pharmacology and Business Development at Psychogenics Inc., a preclinical contract research organization. From 1999 to 2003, she was the Research Director of In Vivo Pharmacology at Arena Pharmaceuticals, Inc. (Nasdaq: ARNA), leading a multidisciplinary research team. Prior to that, Dr. Menzaghi established and directed a preclinical research laboratory at SIBIA Neurosciences (acquired by Merck). Her research expertise ranged from the development of small molecules to small peptides. She has extensive experience with corporate partnering with large U.S. and Asian pharmaceutical companies including Eli Lilly, Merck and J&J. Dr. Menzaghi received her Ph.D. in Neurosciences from the University of Louis Pasteur, Strasbourg, France and her M.Sc. in clinical psychology from the University of Nancy, France, after which she conducted her post-doctoral research at the Scripps Research Institute, San Diego, California. She has over 55 peer-reviewed publications and book chapters, 100 international meeting presentations and is listed as an inventor on numerous patents.

Joana Goncalves, M.D. Dr. Goncalves has served as our Chief Medical Officer since October 2018. Prior to joining Cara, Dr. Goncalves worked at Celgene Corporation from April 2014 to October 2018, where she most recently served as Vice President, Medical Affairs for Dermatology and Neurology and was instrumental in planning and executing medical support activities for a number of programs, including OTEZLA® for psoriasis. Previously, Dr. Goncalves held the position of Vice President, Medical Strategy and Scientific Affairs at LEO Pharma Inc., the U.S. subsidiary of LEO Pharma A/S, a global healthcare company specializing in dermatology and critical care, from February 2012 to April 2014. She began her pharmaceutical career at Novartis Pharmaceuticals, working on a range of products across various therapeutic areas from 2001 to 2012. Dr. Goncalves received her M.D. from the University of Cape Town, South Africa.

Scott M. Terrillion. Mr. Terrillion has served as our General Counsel, Secretary and Chief Compliance Officer since November 2016. Mr. Terrillion brings over 20 years of diverse pharmaceutical industry experience from varying legal and business roles in the public, private and not-for-profit sectors. Mr. Terrillion spent 15 years at Boehringer Ingelheim Pharmaceuticals, Inc., a research-driven pharmaceutical company, where he served as Vice President, Associate General Counsel. At Boehringer, Mr. Terrillion built and led the legal team supporting the global company's U.S. human pharmaceutical business during a period of rapid, industry-leading growth. Mr. Terrillion also spent two years at Mesoblast, Inc., a publicly traded emerging biotech, as the company's Vice President, Associate General Counsel and Head of Compliance. Mr. Terrillion began his legal career at Nixon, Hargrave, Devans & Doyle (now Nixon Peabody LLP), a large general practice law firm, where he was an associate in the Health Care and Technology/Intellectual Property Practice groups. A licensed pharmacist, Mr. Terrillion began his professional career as a community pharmacist and later served as Director of Pharmacy for Preferred Care, Inc., an HMO insurance provider. Mr. Terrillion received his B.S. in Pharmacy from the Albany College of Pharmacy and Health Sciences, where he serves on the Board of Trustees, and a Juris Doctor, magna cum laude, from Albany Law School. He is a member of the New York bar and authorized house counsel in Connecticut.

The following table sets forth certain information with respect to our non-employee directors as of March 1, 2019:

Name	Age	Position
Martin Vogelbaum	55	Director
Harrison M. Bains, Jr.	75	Director
Jeffrey Ives, Ph.D.	68	Director
Christopher Posner	49	Director

Martin Vogelbaum. Mr. Vogelbaum has served as a member of our Board of Directors since July 2010. He currently serves as Managing Partner of Inning One Ventures, a life science venture capital fund. Previously, Mr. Vogelbaum served as Corporate Vice President, Business Development at Celgene Corporation from 2015 to 2017.
Mr. Vogelbaum served as a partner of Rho Ventures from 2005 until 2015 and again from 2017 to 2018, where he focused on investments in biotechnology, biopharmaceuticals and medical devices. He has more than 25 years of experience investing in the life sciences sector, having been involved with companies at all stages of development, including co-founding more than a half dozen companies. Prior to his venture capital career, he was a research associate in the bone marrow transplantation unit at Memorial-Sloan Kettering Hospital, where he conducted research in graft-versus-host-disease. Mr. Vogelbaum previously served as a director of Inotek Pharmaceuticals Corporation

(Nasdaq: ITEK) from 2010 to 2016 and NephroGenex, Inc. (Nasdaq: NRX) from 2013 to 2014. He currently serves on the Healthcare Advisory Board for the Partnership Fund for New York City as well as the Scientific Advisory Committee for Weill Cornell Medical College's Daedalus Fund for Innovation. Mr. Vogelbaum received his A.B. in biology and history from Columbia University. Mr. Vogelbaum's experience in the life sciences industry as a venture capitalist provides him with the qualifications and skills to serve on our Board of Directors.

Harrison M. Bains, Jr. Mr. Bains has served as a member of our Board of Directors since July 2014. Mr. Bains served in multiple roles at Bristol Myers Squibb Company, including Vice President, Treasurer and acting Chief Financial Officer from 1988 through his retirement in 2004. Mr. Bains's career also includes serving as Senior Vice President of the Primary Industries group at Chase Manhattan Bank and 11 years with RJR Nabisco and two of its predecessor companies as Senior Vice President and Treasurer. He currently serves as a director and chair of the Audit Committee of the Mercer Funds, Inc., a registered investment company. He has served as a member of the board of trustees of the Park Avenue Armory since October 2007 and the Civil War Trust since September 2007, and previously served as a member of the board of trustees of the University of Redlands from October 1989 to May 2013, as a member of the board of directors of BG Medicine, Inc. from 2007 to 2015, and as a member of the Board of Directors of Bank of America Funds from 2010 to 2016. Mr. Bains earned an M.B.A from the University of California, Berkeley and a B.A. in economics from the University of Redlands. He also completed the Advanced Management Program at Harvard Business School. His extensive experience in the biotechnology industry provides him with the qualifications to serve on our Board of Directors.

Jeffrey L. Ives, Ph.D. Dr. Ives has served as a member of our Board of Directors since July 2014. Dr. Ives currently is a Venture Partner at New Leaf Venture Partners, healthcare technology venture firm, and a Principal at NeuroPharma Advisors, LLC., an advisory group focused on companies developing therapeutics for the CNS. Dr. Ives is also currently a director at private pharmaceutical and biotechnology companies, Astrocyte Pharmaceuticals Inc., Acumen Pharmaceuticals, Inc., Pinteon Therapeutics Inc. and Orthogonal Neurosciences, private. Previously, Dr. Ives served as the Chief Executive Officer of Satori Pharmaceuticals, Inc., a neurodegenerative disease company focused on discovery and development of breakthrough therapies for the treatment and prevention of Alzheimer's disease from 2008 until 2013. Prior to Satori, Dr. Ives led the CNS, pain and oncology research teams at Pfizer for over two decades and, from 2001 to 2007, he served as a Senior Vice President leading the global Pharmacokinetics, Dynamics and Metabolism organization. Dr. Ives received his doctorate and master degrees from Yale University and received his bachelor of arts degree from Colgate University. His extensive experience leading research and drug development provides him with the qualifications to serve on our Board of Directors.

Christopher Posner. Mr. Posner has served as a member of our Board of Directors since August 2018. Mr. Posner has broad experience in commercial and marketing operations and product management at both large and specialty pharmaceutical companies, where he has focused on products for autoimmune, inflammatory and pain conditions, including Xeljanz® and Enbrel®. Since July 2017, he has been the Chief Executive Officer of LEO Pharma, Inc. US, a subsidiary of LEO Pharma A/S, a global healthcare company specializing in dermatology and critical care, including such conditions as psoriasis and atopic dermatitis. Prior to joining LEO, he was the Head of Worldwide Commercial Operations at R-Pharma-US, LLC, a specialty pharmaceutical company focused on oncology and chronic immune disorders, from 2014 until 2017. Previously, Mr. Posner held a variety of senior management positions in commercial and marketing operations at Bristol-Myers Squibb Company, Pfizer Inc., Wyeth Pharmaceuticals, Inc. and Endo Pharmaceuticals plc. Mr. Posner holds an M.B.A. from Fuqua School of Business, Duke University and a B.A. in Economics from Villanova University. Mr. Posner's extensive experience in the pharmaceutical industry, including in commercial and marketing operations, provides him with the qualifications to serve on our Board of Directors.

Audit Committee

The Audit Committee of the Board of Directors was established by the Board in accordance with Section 3(a)(58)(A) of the Exchange Act, to oversee our corporate accounting and financial reporting processes and audits of our financial statements. For this purpose, the Audit Committee performs several functions. The Audit Committee evaluates the performance of and assesses the qualifications of the independent auditors; determines and approves the engagement of the independent auditors; determines whether to retain or terminate the existing independent auditors or to appoint and engage new independent auditors; reviews and approves the retention of the independent auditors to perform any proposed permissible non-audit services; monitors the rotation of partners of the independent auditors on our audit

engagement team as required by law; reviews and approves or rejects transactions between us and any related persons; confers with management and the independent auditors regarding the effectiveness of internal controls over financial reporting, the objectivity of our financial reporting and our accounting policies and practices; establishes procedures, as required under applicable law, for the receipt, retention and treatment of complaints received by us regarding accounting, internal accounting controls or auditing matters and the confidential and anonymous submission by employees of concerns regarding questionable accounting or auditing matters; and meets to review our annual audited financial statements and quarterly financial statements with management and the independent auditor, including a review of our disclosures under “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

The Audit Committee is composed of three directors: Mr. Vogelbaum, Mr. Bains and Mr. Posner. In 2018, Dr. Ives also served on the Audit Committee from January through August. Upon joining our Board of Directors in August 2018, Mr. Posner was appointed and replaced Dr. Ives as a member of the Audit Committee. The Audit Committee met four times during the fiscal year ended December 31, 2018.

The Board of Directors reviews the Nasdaq listing standards definition of independence for Audit Committee members on an annual basis and has determined that all members of our Audit Committee are independent, as defined in Rule 5605(c)(2)(A)(i) and (ii) of the Nasdaq listing standards and Rule 10A-3 of the Exchange Act, and that each such member meets the financial literacy requirements of Nasdaq.

The Board of Directors has also determined that Mr. Bains qualifies as an "audit committee financial expert," as defined in applicable SEC rules. The Board made a qualitative assessment of Mr. Bains's level of knowledge and experience based on a number of factors, including his formal education and experience as acting chief financial officer for a public reporting company.

Code of Ethics and Business Conduct

Our Board of Directors has adopted a Code of Business Conduct and Ethics that applies to all officers, directors and employees. The Code of Business Conduct and Ethics is available on our website at www.caratherapeutics.com in the News & Investors section under Corporate Governance. If we make any substantive amendments to the Code of Business Conduct and Ethics or grant any waiver from a provision of the Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our directors and executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock and other equity securities. Officers, directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2018, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with.

Item 11. Executive Compensation.

Cara is an "emerging growth company," as defined in Section 101(a)(19)(C) of the JOBS Act. As an emerging growth company, under SEC rules, we are not required to include a Compensation Discussion and Analysis section in this Item 11 and have elected to comply with reduced compensation disclosure requirements, as permitted under the JOBS Act.

2018 Summary Compensation Table

The following table shows for the fiscal years ended December 31, 2018, 2017 and 2016, compensation awarded to or paid to, or earned by, our Chief Executive Officer, our two other most highly compensated executive officers at December 31, 2018 and our former Chief Medical Officer. We refer to these individuals as our Named Executive Officers.

Name and Principal Position	Year	Salary	Bonus [1]	Stock Awards [2]	Option Awards [3]	Non-Equity Incentive Plan Compensation	All Other Compensation [4]	Total Compensation [5]
Derek Chalmers, Ph.D., D.Sc. [6]	2018	$542,100	$—	$ —	$1,997,623	$ 238,524	$ 10,799	$2,789,046
President and Chief Executive Officer	2017	526,300	—	—	2,753,848	233,400	8,100	$3,521,648
	2016	511,000	—	—	736,837	204,400	7,950	1,460,187
Joana Goncalves, M.D. [7] Chief Medical Officer	2018	82,639	60,000	—	3,560,536	32,603	413	3,736,191
Frédérique Menzaghi, Ph.D. Chief Scientific Officer and Senior Vice President, R&D	2018	400,000	—	—	615,428	212,000	10,799	1,238,227
	2017	379,935	—	—	917,949	200,000	8,100	1,505,984
	2016	357,000	—	—	246,878	168,682	7,950	780,510
Joseph Stauffer, D.O. [8] Former Chief Medical Officer	2018	368,900	141,895	—	615,428	—	567,627	1,693,850
	2017	426,000	—	—	917,949	170,400	8,875	1,523,224
	2016	414,000	—	—	250,676	223,560	8,199	896,435

(1) The amount disclosed in this column represent a one-time bonus, payable on the first regularly scheduled payroll date following the executive officer's start date.

(2) In accordance with SEC rules, these amounts reflect the grant date fair values of the restricted stock units, or RSUs, granted to each of Drs. Chalmers, Menzaghi and Stauffer in 2018, calculated in accordance with ASC Topic 718 for stock-based compensation transactions, based on the probable outcome of the vesting conditions of these RSUs as of the grant date. Each RSU represented the contingent right to receive one share of our common stock upon the achievement of certain performance targets through the first quarter of 2019, subject to the recipient's continuous service through the vesting events. As of the grant date, the performance vesting condition was considered not probable of occurring and, as a result, the grant date fair value of the RSUs, for purposes of this table, is $0. Assuming that the performance vesting condition of these RSUs was met as of the grant date, the value of these

RSUs would have been $772,446 for Dr. Chalmers and $238,054 for each of Drs. Menzaghi and Stauffer. The performance vesting condition for these RSUs was met in December 2018, and the actual value of these RSUs upon vesting in full was $495,344 for Dr. Chalmers and $152,656 for each of Drs. Menzaghi and Stauffer. See Note 13 to our financial statements included in this Annual Report on Form 10-K for a further description of our valuation methodology for equity awards.

(3) The amounts disclosed in this column are the fair value on the grant date of each award granted under our 2014 Plan, computed in accordance with ASC 718, using the valuation methodology for equity awards set forth in Note 13 of our financial statements included in this Annual Report on Form 10-K. All of the options awards reported in the table above were granted under our 2014 Plan and have a term of ten years from the date of grant. Stock options granted to officers and employees in 2018, 2017 and 2016, who had previously been granted stock options, vest monthly over a four-year period from the grant date. The initial grant of stock options to officers and employees vests 25% after the first year and ratably thereafter during the following 36 months.

(4) The amounts disclosed in this column represent the annual cash incentive bonus earned by the named executive officer for services performed in 2018, 2017 and 2016. The 2018 annual incentive bonus will be paid in March 2019. The 2017 annual incentive bonus was paid in February 2018. The 2016 annual incentive bonus was paid in March 2017. The annual cash incentive bonus for each executive officer is based on the Board's assessment of each such officer's individual performance and our overall performance against objectives determined by our Board and communicated to such officer. For the fiscal years ended December 31, 2018, 2017 and 2016, the annual cash incentive bonuses were based on our achievement of clinical, regulatory, financial and operational objectives. See "—Executive Employment Arrangements and Potential Payments upon Termination or Change in Control" below for additional information regarding assigned bonus targets, expressed as a percentage of each executive officer's base salary.

(5) All other compensation for 2017 and 2016 includes $8,100 and $7,950, respectively, for 401(k) Employee Benefit Plan contributions we made to the account of each of Drs. Chalmers, Menzaghi and Stauffer under the ERISA Safe Harbor Rules, representing the same percentage of salary as contributed to all employee accounts, up to a maximum amount of salary. For 2017 and 2016, all other compensation also includes $775 and $249 for tax gross-ups for Dr. Stauffer related to hotel accomodations close to our headquarters for 2017 and 2016. For our named executive officers other than Dr. Stauffer, this column also includes the following for 2018: (i) $8,250 for 401(k) Employee Benefit Plan contributions we made to the account of each of Drs. Chalmers and Menzaghi under the ERISA Safe Harbor Rules; (ii) $1,800 for parking for each of Dr. Chalmers and Dr. Menzaghi; (iii) $300 for parking for Dr. Goncalves; (iv) $749 for life insurance payments for each of Dr. Chalmers and Dr. Menzaghi; and (v) $113 for life insurance payments for Dr. Goncalves.

(6) Dr. Chalmers is also a member of our Board of Directors but does not receive any additional compensation in his capacity as a director.

(7) Dr. Goncalves joined Cara on October 22, 2018. For the year ended December 31, 2018, the amounts reported as salary and non-equity incentive plan compensation, represents Dr. Goncalves's base salary paid from October 22, 2018 to December 31, 2018 and her prorated annual cash incentive bonus.

(8) Dr. Stauffer served as our Chief Medical Officer until October 22, 2018 (the "Separation Date"). Salary reported for Dr. Stauffer for 2018 represents his salary earned through the Separation Date. Bonus reported for Dr. Stauffer for 2018 represents the prorated amount of his 2018 target bonus, which was payable pursuant to the Separation and Consulting Agreement we entered into with Dr. Stauffer as of the Separation Date. All other compensation for Dr. Stauffer for 2018 includes: (i) the intrinsic value of stock options for which vesting was accelerated to the Separation Date in the amount of $465,432; (ii) $85,000 of consulting fees payable to Dr. Stauffer for services provided to us from the Separation Date through December 31, 2018; (iii) $5,968 of COBRA insurance premium reimbursements; (iv) $8,250 for 401(k) Employee Benefit Plan contributions we made to the account of Dr. Stauffer under the ERISA Safe Harbor Rules; (v) $1,500 for parking; (vi) $624 for life insurance payments and (vii) $853 for tax gross-ups for Dr. Stauffer related to hotel accommodations close to our headquarters for 2018.

Outstanding Equity Awards at December 31, 2018

The following table shows certain information regarding outstanding equity awards held by our Named Executive Officers at December 31, 2018.

Name	Number of Securities Underlying Unexercised Options Exercisable	Number of Securities Underlying Unexercised Options Unexercisable		Option Exercise Price	Option Expiration Date
Derek Chalmers, Ph.D., D.Sc.	80,000	—	(1)	$ 11.00	1/30/2024
President and Chief Executive Officer	158,125	6,875	(2)	10.82	6/15/2025
	130,375	60,625	(2)	6.00	3/30/2026
	98,437	126,563	(2)	17.41	3/8/2027
	35,156	152,344	(2)	14.39	3/9/2028
Joana Goncalves, M.D.	—	250,000	(1)	19.27	10/22/2028
Chief Medical Officer					
Frédérique Menzaghi, Ph.D.					
Chief Scientific Officer and Senior Vice President, R&D	40,000	—	(1)	11.00	1/30/2024
	57,500	2,500	(2)	10.82	6/15/2025
	44,687	20,313	(2)	6.00	3/30/2026
	32,812	42,188	(2)	17.41	3/8/2027
	10,828	46,922	(2)	14.39	3/9/2028
Joseph Stauffer, D.O.	180,000	—		8.74	12/1/2024(4)
Former Chief Medical Officer	66,000	—		6.00	3/30/2026(4)
	64,008	10,992	(3)	17.41	3/8/2027(4)
	10,827	46,923	(3)	14.39	3/9/2028(4)

(1) Shares underlying these stock options vest over a four-year period as follows: 25% of the shares underlying the option vest on the first anniversary of the date of grant, with the remainder vesting in equal monthly installments over the 36 months thereafter.

(2) Shares underlying these stock options vest monthly over a four-year period from the grant date.

(3) The exercisable shares give effect to the acceleration of vesting of certain stock options in connection with Dr. Stauffer's separation as our Chief Medical Officer during 2018. The remaining unvested shares underlying these options continue vesting during the term of Dr. Stauffer's consulting agreement with us, which we expect will end on July 22, 2019, in accordance with the original vesting terms of the award, with 1/48th of the total shares subject

to each grant vesting on a monthly basis through the termination of Dr. Stauffer's consulting term. See "--Executive Employment Arrangements and Potential Payments upon Termination or Change in Control—Separation With Dr. Stauffer."

(4) Based on the term of Dr. Stauffer's consulting agreement, it is expected that these awards will expire on October 22, 2019, three months after the expected conclusion of his consulting term, if not previously exercised.

Executive Employment Arrangements and Potential Payments upon Termination or Change in Control

We have entered into employment agreements with each of Drs. Chalmers, Goncalves and Menzaghi. Under these employment agreements, the executive officers' respective initial annual salaries and target annual bonuses are subject to review and adjustment from time to time by the Board of Directors in its sole discretion.

For the year ended December 31, 2018, our Named Executive Officers' respective annual salaries and target annual bonuses were:

Executive Officer	2018 Base Salary	Target Bonus (as a % of Base Salary)
Dr. Chalmers	$ 542,100	55%
Dr. Goncalves	425,000	40%
Dr. Menzaghi	400,000	40%
Dr. Stauffer	439,200	40%

Under these employment agreements, each executive officer is eligible for severance benefits in specified circumstances. Under the terms of the agreements, upon execution and effectiveness of a general release of claims, each executive officer will be entitled to severance payments if we terminate his or her employment without cause, or in the case of Dr. Chalmers, the employee terminates employment with us for good reason. The following definitions have been adopted in these employment agreements:

- "cause" means that we have determined in our sole discretion that any of the following occurred: (a) the executive officer's commission of a felony; (b) the executive officer's act or omission constituting dishonesty, fraud, immoral, or disreputable conduct that causes material harm to us; (c) the executive officer's violation of a company policy that causes material harm to us; (d) the executive officer's material breach of the employment agreement, or of any provision of any other agreement between the executive officer and us which, if curable, is not cured within 30 days after notice thereof is given to the executive officer, or (e) the executive officer's breach of fiduciary duty;
- "good reason" means any of the following without the executive officer's prior written consent: (a) the assignment to the executive officer of duties or responsibilities that would result in the material diminution of the executive officer's then-current position, with the exception of certain situations involving the acquisition of us; (b) a reduction of the executive officer's annual base salary by greater than 30%, except in a situation in which the base salaries of other similarly situated employees are accordingly reduced; or (c) any request that the executive officer relocate to a new principal base of operations that would increase the executive officer's one-way commute distance by more than 100 miles, unless the executive officer accepts the relocation opportunity.
- "change in control" means any of the following: (a) any person becomes the owner, directly or indirectly, of securities representing more than 50% of our combined voting power other than through a merger, consolidation or similar transaction, subject to specified exceptions; (b) a merger or consolidation, unless the holders of our outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing more than 50% of our voting power or other entity surviving such transaction, subject to specified exceptions; (c) a sale, lease, exclusive license or other disposition of all or substantially all of our assets, other than the transfer of our assets to an entity of which our stockholders own more than 50% of the voting power, subject to specified

exceptions; or (d) the directors at the time of our initial public offering, or the incumbent board, cease to constitute at least a majority of the Board of Directors, provided, that new directors that are approved or recommended by the majority of the incumbent board will be considered to be a member of the incumbent board for this purpose.

The following table summarizes the schedule of severance payments and acceleration of unvested equity awards our Named Executive Officers would receive in the event of a qualifying termination:

Scenario and Executive	Salary [1]	Payment of Employer Health Insurance Continuation [1]	Bonus [1]	Acceleration of Unvested Equity Awards
Other Than Within 12 Months Following a Change in Control:				
Dr. Chalmers	12 months	12 months	Prorated Target Bonus	None
Dr. Goncalves	9 months	9 months	50% of Target Bonus	None
Dr. Menzaghi	6 months	6 months	Prorated Target Bonus	None
Within 12 Months Following a Change in Control:				
Dr. Chalmers	12 months	12 months	Prorated Target Bonus	100% Acceleration [2]
Dr. Goncalves	9 months	9 months	50% of Target Bonus	50%-100% Acceleration [3]
Dr. Menzaghi	6 months	6 months	Prorated Target Bonus	100% Acceleration [2]

(1) Subject to the execution of a general release by the relevant executive officer, on the 60th day following termination without cause or, in the case of Dr. Chalmers, resignation for good reason, we will pay such payments relating to base salary, target bonus and health insurance premiums in a lump sum that this executive officer would have received on or prior to such date under the original schedule (less applicable withholdings and deductions), with the balance of such payments being paid as originally scheduled.

(2) The executive officer will receive accelerated vesting of 100% of his or her then unvested equity awards, if any, upon a qualifying termination that occurs within 12 months of the change in control.

(3) The executive officer will receive accelerated vesting of (a) 50% of her then unvested equity awards, if any, upon a qualifying termination that occurs within six months following the change in control and (b) 100% of her then unvested equity awards, if any, upon a qualifying termination that occurs between six and twelve months of the change in control.

Separation With Dr. Stauffer

We entered into a Separation and Consulting Agreement with Dr. Stauffer, effective October 22, 2018, in connection with his separation as Chief Medical Officer. Pursuant to the terms of our separation with Dr. Stauffer, he received a prorated target bonus for 2018 and accelerated vesting of 63,446 stock options (representing 50% of his outstanding unvested stock options as of October 22, 2018). We also engaged Dr. Stauffer as a consultant for a nine-month period, during which he is providing consulting services related to our programs in postoperative pain and PONV in return for a consulting fee of $36,600 per month. Pursuant to our separation agreement with Dr. Stauffer, we also

agreed to reimburse COBRA insurance premium payments made by Dr. Stauffer for up to nine months.

2014 Equity Incentive Plan

Our Board of Directors and our stockholders approved and adopted our 2014 Equity Incentive Plan, or the 2014 Plan, in January 2014. 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, or collectively, 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.

Initially, the aggregate number of shares of our common stock that may be issued pursuant to stock awards under the 2014 Plan was 1,600,000 shares. Additionally, the number of shares of our common stock reserved for issuance under the 2014 Plan has automatically increased on January 1 of each year, beginning on January 1, 2015 and continuing through and including January 1, 2024, by 3% of the total number of shares of our capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by our Board of Directors. On January 1, 2019, the aggregate number of shares of common stock that may be issued pursuant to stock awards under our 2014 Equity Incentive Plan automatically increased to 6,086,907. 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.

2004 Stock Incentive Plan

Our Board of Directors adopted, and our stockholders subsequently approved, the Cara Therapeutics 2004 Stock Incentive Plan, or the 2004 Plan, in September 2004. The 2004 Plan provides for the grant to our officers, directors, employees, consultants and advisors of incentive and nonqualified stock options to purchase our common stock, and also provides for the outright issuance of our common stock through restricted share awards. Since the effectiveness of the 2014 Plan in January 2014, no further awards have been allowed to be granted under the 2004 Plan.

401(k) Plan

We maintain the Cara Therapeutics Savings and Retirement 401(k) Plan, or the 401(k) Plan, a tax-qualified retirement plan that provides eligible U.S. employees with an opportunity to save for retirement on a tax advantaged basis. 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 Internal Revenue Code limit. Pre-tax contributions are allocated to each participant’s individual account and are then invested in selected investment alternatives according to the participant’s directions. Contributions that we may make are subject to a vesting schedule; employees are immediately and fully vested in their contributions. The 401(k) Plan is intended to qualify under Sections 401(a) and 501(a) of the Code. As a tax-qualified retirement plan, contributions to the 401(k) Plan and earnings on those contributions are not taxable to the employees until distributed from the 401(k) Plan and all contributions are deductible by us when made.

Director Compensation

The following table shows certain information with respect to the compensation of all of our non-employee directors for the fiscal year ended December 31, 2018:

Director	Fees paid in cash [1]	Option awards [2]	Total
Martin Vogelbaum	$108,000	$224,261	$332,261
Harrison M. Bains, Jr.	$60,000	$224,261	$284,261
Jeffrey Ives, Ph.D.	$57,000	$224,261	$281,261

Christopher Posner (3)	$24,000	$470,289	$494,289
Dean Slagel (4)	$10,000	$—	$10,000

(1) This column includes the annual fees paid to all non-employee directors for their service on the Board of Directors as well as for their committee membership and chairmanship.

(2) The amounts disclosed in this column represent the aggregate grant date fair value of the stock options granted, computed in accordance with FASB ASC Topic 718, using the valuation methodology for equity awards set forth in Note 13 of our financial statements included in this Annual Report on Form 10-K. The options granted to Mr. Vogelbaum, Mr. Bains and Dr. Ives have an exercise price per share of $16.07 and were granted on June 6, 2018 in connection with our 2018 Annual Meeting of Stockholders. The options granted to Mr. Posner have an exercise price of $17.94 and were granted on August 2, 2018 in connection with his appointment to our Board of Directors.

(3) Mr. Posner was appointed to the Board of Directors, effective August 2, 2018.

(4) Mr. Slagel resigned from the Board of Directors, effective March 7, 2018.

The options for Mr. Vogelbaum, Mr. Bains and Dr. Ives described in the table above vest on the one-year anniversary of the grant date, subject to the director's continued service as a director through such date. The options for Mr. Posner described in the table above vest over a three-year period in equal installments from the date of the grant, subject to Mr. Posner's continued service as a director through each such vesting date. As of December 31, 2018, options to purchase 81,500 shares of common stock were held by Mr. Vogelbaum, Mr. Bains and Dr. Ives, of which 63,500 underlying shares were vested and immediately exercisable, and an option to purchase 35,000 shares of common stock was held by Mr. Posner, of which none of the underlying shares were vested or immediately exercisable.

Directors who are also full-time officers or employees of Cara do not receive any additional compensation for serving as directors. Therefore, Dr. Chalmers, our Chief Executive Officer and one of our directors, does not receive any additional compensation for his service as a director. Dr. Chalmers' compensation as an executive officer is set forth above under "2018 Summary Compensation Table."

Our Board of Directors has adopted a non-employee director compensation policy. Under our director compensation policy, we will pay each of our non-employee directors a cash retainer for service on our Board of Directors and for service on each committee on which the director is a member. These retainers are payable in arrears in four equal quarterly installments on the last day of each quarter, provided that the amount of such payment will be prorated for any portion of such quarter that the director is not serving on our Board of Directors. The retainers paid during 2018 to non-employee directors for service on our Board of Directors and for service on each committee of our Board of Directors on which the director is a member were as follows:

	Member Annual Service Retainer	Chairman Additional Annual Service Retainer	
Board of Directors	$ 40,000	$ 35,000	(1)
Audit Committee	$ 10,000	$ 10,000	
Compensation Committee	$ 7,500	$ 7,500	
Nominating and Corporate Governance Committee	$ 4,000	$ 4,000	

(1) During the year ended December 31, 2018, our Board of Directors had a Lead Independent Director rather than a Chairman. For the year ended December 31, 2018, the Lead Independent Director received an additional retainer of

$35,000.

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We also reimburse our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending our Board of Directors and committee meetings. In addition, under our director compensation policy, upon initial election to the Board of Directors, each non-employee director will receive an option to purchase 35,000 shares with an exercise price equal to the fair market value of our common stock on the date of grant. Such option vests over three years in equal annual installments, subject to the director's continued service as a director through each such vesting date. Further, on the date of each annual meeting of stockholders, each non-employee director that continues to serve as a non-employee member on our Board of Directors will receive an option to purchase 18,000 shares of our common stock with an exercise price equal to the fair market value of our common stock on the date of grant. Such option will vest on the earlier of the first-year anniversary of the date of grant and our next annual meeting of stockholders, subject to the director's continued service as a director through such vesting date.

This policy is intended to provide a total compensation package that enables us to attract and retain qualified and experienced individuals to serve as directors and to align our directors' interests with those of our stockholders.

Compensation Committee Interlocks and Insider Participation

The Compensation Committee is composed of three directors: Mr. Vogelbaum, Dr. Ives and Mr. Posner. None of the current members of the Compensation Committee has at any time during the past three years been one of our officers or employees. None of our executive officers currently serves or in the prior three years has served as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving on the Board or Compensation Committee.

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

The following table sets forth certain information regarding the ownership of our common stock as of March 1, 2019 by: (i) each director; (ii) each of the individuals named in the 2018 Summary Compensation Table; (iii) all of our current executive officers and directors as a group; and (iv) all those known by us to be beneficial owners of more than five percent of our common stock.

Name of beneficial owner	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
5% stockholders:		
Rho Ventures VI, LP [1]	3,568,057	9.0 %
Blackrock, Inc. [2]	2,800,605	7.1
T. Rowe Price [3]	2,415,491	6.1
State Street Corporation [4]	2,123,225	5.4
Directors and named executive officers:		
Derek Chalmers, Ph.D., D.Sc. [5]	1,513,297	3.8
Joana Goncalves, M.D.	—	*
Frédérique Menzaghi, Ph.D [6]	349,085	*

Joseph Stauffer, D.O. [7]	371,378	*	
Martin Vogelbaum [8]	63,500	*	
Harrison M. Bains, Jr. [8]	63,500	*	
Jeffrey Ives, Ph.D. [8]	63,500	*	
Christopher Posner	—	*	
All current executive officers and directors as a group (9 persons) [9]	2,289,781	5.6	%

*Less than one percent.

This table is based upon information supplied by officers, directors and principal stockholders and Schedules 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned. Applicable percentages are based on 39,547,558 shares outstanding on March 1, 2019. In computing the number of shares of common stock beneficially owned by a person and the percentage ownership of that person, we have deemed outstanding shares of common stock subject to options held by that person that are exercisable within 60 days after March 1, 2019. We have not deemed these shares outstanding, however, for the purpose of computing the percentage ownership of any other person.

Except as otherwise noted below, the address for each person or entity listed in the table is c/o Cara Therapeutics, Inc., 4 Stamford Plaza, 107 Elm Street, Stamford, Connecticut 06902.

(1) Based solely on Schedule 13G filed on February 9, 2018 by Rho Ventures VI, L.P. The general partner of Rho Ventures VI, L.P. ("RV VI") is RMV VI, L.L.C., a Delaware limited liability company, and the managing member of RMV VI, L.L.C. is Rho Capital Partners LLC, a Delaware limited liability company ("RCP LLC"). Each of Habib Kairouz, Mark Leschly and Joshua Ruch is a managing member of RCP LLC, and in their capacity as such may be deemed to exercise voting and investment power over the shares held by the Rho Funds. Martin Vogelbaum is one of our directors and is a non-managing member of RMV VI, L.L.C. The address of Rho Capital Partners, LLC, RMV VI, L.L.C. and RV VI is 152 West 57th Street, 23rd Floor, New York, NY 10019.

(2) Based solely on Schedule 13G filed by BlackRock, Inc. on February 4, 2019. BlackRock, Inc. has sole voting power as to 2,733,548 of the shares and sole dispositive power as to all of the shares. The address of BlackRock, Inc. is 55 East 52nd Street, New York, NY 10055.

(3) Based solely on Schedule 13G filed by T. Rowe Price Associates, Inc. on February 14, 2019. T. Rowe Price Associates, Inc. has sole voting power as to 323,875 of the shares and sole dispositive power as to all of the shares. The address of T. Rowe Price Associates, Inc. is 100 E. Pratt Street, Baltimore, MD 21202.

(4) Based solely on Schedule 13G filed by State Street Corporation on February 14, 2019. State Street Corporation has sole voting power as to none of the shares and sole dispositive power as to none of the shares. The address of State Street Corporation is State Street Financial Center, One Lincoln Street, Boston, MA 02111.

(5) Consists of 953,788 shares held directly by Dr. Chalmers and 559,509 shares of common stock underlying options that are vested and exercisable within 60 days of March 1, 2019.

(6) Consists of 144,279 shares held directly by Dr. Menzaghi and 204,806 shares of common stock underlying options that are vested and exercisable within 60 days of March 1, 2019.

(7) Consists of 13,779 shares of common stock held directly by Dr. Stauffer and 357,599 shares of common stock underlying options that are vested and exercisable within 60 days of March 1, 2019.

(8) Consists of 63,500 shares of common stock underlying options that are vested and exercisable within 60 days of March 1, 2019.

(9) Consists of the shares listed in footnotes (5), (6) and (8); also includes (i) 8,026 shares held directly by Mani Mohindru, Ph.D., our Chief Financial Officer and 128,332 shares of common stock underlying options held by Dr. Mohindru that are vested and exercisable within 60 days of March 1, 2019 and (ii) 6,386 shares held directly by Scott Terrillion, our General Counsel, Secretary and Chief Compliance Officer, and 94,155 shares of common stock underlying options held by Mr. Terrillion that are vested and exercisable within 60 days of March 1, 2019.

Securities Authorized for Issuance under Equity Compensation Plans

The following table summarizes our equity compensation plan information as of December 31, 2018. Information is included for equity compensation plans approved by our stockholders. We do not have any equity compensation plans not approved by our stockholders.

Plan Category	Number of shares of common stock to be issued upon exercise of outstanding options (a)(1)	Weighted-average exercise price of outstanding options (b)(2)	Number of shares of common stock remaining available for future issuance under equity compensation plans (excluding shares of common stock reflected in column (a)) (c)(3)
Equity compensation plans approved by stockholders [1] [2]	4,004,422	$ 13.34	236,182
Equity compensation plans not approved by stockholders	—	—	—
Total	4,004,422		236,182

(1) Columns (a) and (b) relate to options granted under the 2014 Plan and the 2004 Plan. Since the effectiveness of the 2014 Plan in January 2014, no further awards have been allowed to be granted under the 2004 Plan. The number of securities in column (c) relates only to the 2014 Plan.

(2) The weighted average exercise price is calculated based solely on outstanding stock options, and does not take into account stock underlying restricted stock units, which have no exercise price.

(3) The aggregate number of shares of 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 our capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by our Board

of Directors. Accordingly, on January 1, 2019, the number of shares of common stock available for issuance under our 2014 Plan increased by 1,186,426 shares pursuant to this provision. This increase is not reflected in the table above.

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

Related Person Transactions Policy and Procedures

In 2014, we adopted a written Related-Person Transactions Policy that sets forth our policies and procedures regarding the identification, review, consideration and approval or ratification of "related-persons transactions." For purposes of our policy only, a "related-person transaction" is a transaction, arrangement or relationship (or any series of similar transactions, arrangements or relationships) in which we and any "related person" are participants involving an amount that exceeds $120,000. Transactions involving compensation for services provided to us as an employee, director, consultant or similar capacity by a related person are not covered by this policy. A related person is any of our executive officers, directors, or more than 5% stockholders, including any of their immediate family members, and any entity owned or controlled by such persons.

Under the policy, where a transaction has been identified as a related-person transaction, management must present information regarding the proposed related-person transaction to the Audit Committee (or, where Audit Committee approval would be inappropriate, to another independent body of the Board) for consideration and approval or ratification. The presentation must include a description of, among other things, the material facts, the interests, direct and indirect, of the related persons, the benefits to us of the transaction and whether any alternative transactions were available. To identify related-person transactions in advance, we rely on information supplied by our executive officers, directors and certain significant stockholders. In considering related-person transactions, the Committee takes into account the relevant available facts and circumstances including, but not limited to (a) the risks, costs and benefits to us, (b) the impact on a director's independence in the event the related person is a director, immediate family member of a director or an entity with which a director is affiliated, (c) the terms of the transaction, (d) the availability of other sources for comparable services or products and (e) the terms available to or from, as the case may be, unrelated third parties or to or from employees generally. In the event a director has an interest in the proposed transaction, the director must recuse himself or herself from the deliberations and approval. The policy requires that, in determining whether to approve, ratify or reject a related-person transaction, the Committee consider, in light of known circumstances, whether the transaction is in, or is not inconsistent with, our best interests and our stockholders, as the Committee determines in the good faith exercise of its discretion.

Certain Related Person Transactions

There were no transactions since January 1, 2017 in which we have participated in which the amount exceeded or will exceed $120,000, and in which any of our directors, executive officers or holders of more than 5% of our capital stock or any members of their immediate family had or will have a direct or indirect material interest, other than compensation arrangements which are described under "Executive Compensation" and "Director Compensation."

Indemnification Agreements

Our amended and restated certificate of incorporation limits the liability of directors to the maximum extent permitted by Delaware law. Delaware law provides that directors of a corporation will not be personally liable for monetary damages for breach of their fiduciary duties as directors, except for liability for any:

- breach of their duty of loyalty to the corporation or its stockholders;
- act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law; or
- transaction from which the directors derived an improper personal benefit.

Our amended and restated certificate of incorporation does not eliminate a director's duty of care and, in appropriate circumstances, equitable remedies, such as injunctive or other forms of non-monetary relief, remain available under Delaware law. These limitations also do not affect a director's responsibilities under any other laws, such as the federal securities laws or other state or federal laws. Our amended and restated bylaws provide that we will indemnify our directors and executive officers, and may indemnify other officers, employees and other agents, to the fullest extent permitted by law. Our amended and restated bylaws also provide that we are obligated to advance expenses incurred by a director or officer in advance of the final disposition of any action or proceeding and also permit us to secure insurance on behalf of any officer, director, employee or other agent for any liability arising out of his or her actions in connection with their services to us, regardless of whether our amended and restated bylaws permit such indemnification. We have obtained a directors' and officers' liability insurance policy.

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We have entered, and intend to continue to enter, into separate indemnification agreements with our directors and executive officers, in addition to the indemnification provided for in our amended and restated bylaws. These agreements, among other things, require us to indemnify our directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of our directors or executive officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request. We believe that these bylaw provisions and indemnification agreements are necessary to attract and retain qualified persons as directors and officers.

The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duties. They may also reduce the likelihood of derivative litigation against directors and officers, even though an action, if successful, might benefit us and our stockholders. A Stockholder's investment may be harmed to the extent we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions.

At present, there is no pending litigation or proceeding involving any of our directors or executive officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

Independence of the Board of Directors

As required under the Nasdaq listing standards, a majority of the members of our Board of Directors must qualify as "independent," as affirmatively determined by the Board of Directors. The Board of Directors consults with our counsel to ensure that the Board's determinations are consistent with relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in pertinent listing standards of Nasdaq, as in effect from time to time.

Consistent with these considerations, after review of all relevant identified transactions or relationships between each director, or any of his or her family members, and us, our senior management and our independent auditors, the Board of Directors has affirmatively determined that the following four directors are independent directors within the meaning of the applicable Nasdaq listing standards: Mr. Vogelbaum, Mr. Bains, Dr. Ives and Mr. Posner. In making this determination, the Board of Directors found that none of these directors or nominees for director had a material or other disqualifying relationship with us.

Item 14. Principal Accountant Fees and Services.

The following table represents aggregate fees billed to us for the fiscal years ended December 31, 2018 and 2017, by Ernst & Young LLP, our principal accountant:

	Year Ended December 31,	
	2018	2017
	(Dollars in thousands)	

Audit fees	$361	(a)	$348	(a)
Audit-related fees	35	(b)	15	(b)
Tax fees	—		—	
All other fees	—		—	
Total	$396		$363	

(a) Audit fees for the years ended December 31, 2018 and 2017 consist of the aggregate fees billed for professional services rendered for (i) the audit of our Annual Report on Form 10-K for that year; (ii) the review of our Quarterly Reports on Form 10-Q for each of the first three quarters of that year; (iii) accounting consultations and (iv) procedures in connection with the filing of Form S-3 with the Securities and Exchange Commission for our follow-on offering of our common stock. See “Equity Compensation Plan Compensation” above.

(b) Audit-related fees for the year ended December 31, 2018 include fees billed for review of the accounting for the VFMCRP license agreement. Audit-related fees for the year ended December 31, 2017 include fees billed for review of the preparation and disclosure of our adoption of Accounting Standards Codification Topic 606, Revenue from Contracts with Customers.

All fees described above for the years ended December 31, 2018 and 2017 were pre-approved by the Audit Committee.

Pre-Approval Policies and Procedures

The Audit Committee has adopted a policy and procedures for the pre-approval of audit and non-audit services rendered by our independent registered public accounting firm, Ernst & Young LLP. The policy generally pre-approves specified services in the defined categories of audit services, audit-related services and tax services up to specified amounts. Pre-approval may also be given as part of the Audit Committee's approval of the scope of the engagement of the independent auditor or on an individual, explicit, case-by-case basis before the independent auditor is engaged to provide each service. The pre-approval of services may be delegated to one or more of the Audit Committee's members, but the decision must be reported to the full Audit Committee at its next scheduled meeting.

The Audit Committee has determined that the rendering of services other than audit services by Ernst & Young LLP is compatible with maintaining the principal accountant's independence.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a)(1) The Financial Statements of Cara Therapeutics, Inc.

(a)(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 thereto.

(a)(3) List of Exhibits

Exhibit No.	Description of Exhibit
3.1(1)	Amended and Restated Certificate of Incorporation.
3.2(2)	Amended and Restated Bylaws.
4.1(3)	Form of Common Stock Certificate.
10.1+(3)	Form of Indemnity Agreement.
10.2+(4)	2004 Stock Incentive Plan, as amended, and forms of Stock Option Agreement thereunder.
10.3+(3)	2014 Equity Incentive Plan.
10.3.1(3)	Form of Stock Option Agreement under 2014 Equity Incentive Plan.

10.3.2[3]	Form of Restricted Stock Unit Award under 2014 Equity Incentive Plan.
10.4[4]	Fourth Amended and Restated Investors Rights Agreement dated April 25, 2013 among the Registrant and certain of its stockholders, as amended.
10.5[4]	Lease Agreement dated September 18, 2006 between the Registrant and Shelton Parrott Associates, L.L.C., as amended.
10.6*[4]	License Agreement dated April 4, 2013 by and between the Registrant and Maruishi Pharmaceutical Co., Ltd.
10.7*[4]	License and API Supply Agreement effective as of April 16, 2012 by and between the Registrant and Chong Kun Dang Pharmaceutical Corp.
10.8[4]	Amendment to License and API Supply Agreement effective as of May 1, 2012 by and between the Registrant and Chong Kun Dang Pharmaceutical Corp.
10.9+[5]	Employment Agreement with Derek Chalmers.

Exhibit No.	Description of Exhibit
10.10+(6)	Employment Agreement with Frédérique Menzaghi.
10.11+†	Employment Agreement with Joana Goncalves.
10.12+(3)	Non-Employee Director Compensation Policy.
10.13+(8)	Employment Agreement with Joseph Stauffer.
10.14+**†	Separation and Consulting Agreement with Joseph Stauffer.
10.15 (9)	Lease Agreement dated December 21, 2015 between the Registrant and Four Stamford Plaza Owner L.L.C.
10.16 (10)	Employment Agreement with Mani Mohindru, Ph.D.
10.17*(11)	License Agreement by and between Cara Therapeutics, Inc. and Vifor Fresenius Medical Care Renal Pharma Ltd.
23.1†	Consent of Ernst & Young, LLP, independent registered public accounting firm.
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 Chief 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 Chief 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. (furnished herewith).
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 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.

** Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

† Filed herewith

(1) Filed as exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.

(2) Filed as exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.

(3) Filed as an exhibit (having the same exhibit number) to Pre-effective Amendment No. 2 to the Registrant's Registration Statement on Form S-1 (Registration No. 333-192230) filed with the Securities and Exchange Commission on January 17, 2014 and incorporated herein by reference.

(4) Filed as an exhibit (having the same exhibit number) to the Registration Statement on Form S-1 Registration No. 333-192230) filed with the Securities and Exchange Commission on November 8, 2013 and incorporated herein by reference.
(5) Filed as exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.
(6) Filed as exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.
(7) Filed as exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.
(8) Filed as exhibit 10.14 to the Registrant's Annual Report on Form 10-K (File No. 001-36279) filed with the Securities and Exchange Commission on March 27, 2015 and incorporated herein by reference.
(9) Filed as exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on December 23, 2015 and incorporated herein by reference.
(10) Filed as exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on August 4, 2017 and incorporated herein by reference.
(11) Filed as exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36279) filed with the Securities and Exchange Commission on August 7, 2018 and incorporated herein by reference.

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 12th day of March 2019.

CARA THERAPEUTICS, INC.

By: /s/ DEREK CHALMERS
Name: Derek Chalmers, Ph.D., D.Sc.
Title: President and Chief Executive Officer

Signature	Title	Date
/s/ DEREK CHALMERS Derek Chalmers, Ph.D., D.Sc.	President, Chief Executive Officer and Director (Principal Executive Officer)	March 12, 2019
/s/ MANI MOHINDRU Mani Mohindru, Ph.D.	Chief Financial Officer (Principal Financial and Accounting Officer)	March 12, 2019
/s/ MARTIN VOGELBAUM Martin Vogelbaum	Director	March 12, 2019
/s/ HARRISON M. BAINS, JR. Harrison M. Bains, Jr.	Director	March 12, 2019
/s/ JEFFREY IVES Jeffrey Ives, Ph.D.	Director	March 12, 2019
/s/ CHRISTOPHER POSNER Christopher Posner	Director	March 12, 2019

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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders 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, 2018 and 2017, and the related statements of comprehensive loss, and stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, 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 as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

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

Stamford, Connecticut

March 12, 2019

Cara Therapeutics, Inc.

Balance Sheets

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

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	$15,081	$9,388
Marketable securities	146,302	83,181
Income tax receivable	664	731
Other receivables	926	123
Prepaid expenses	4,805	1,635
Restricted cash, current	361	—
Total current assets	168,139	95,058
Marketable securities, non-current	21,396	—
Property and equipment, net	880	1,177
Restricted cash	408	769
Total assets	$190,823	$97,004
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	$13,622	$8,506
Current portion of deferred revenue	26,825	—
Total current liabilities	40,447	8,506
Deferred revenue, non-current	15,184	—
Deferred lease obligation	1,562	1,718
Commitments and contingencies (Note 17)	—	—
Stockholders' equity:		
Preferred stock; $0.001 par value; 5,000,000 shares authorized at December 31, 2018 and December 31, 2017; zero shares issued and outstanding at December 31, 2018 and December 31, 2017	—	—
Common stock; $0.001 par value; 100,000,000 shares authorized at December 31, 2018 and December 31, 2017; 39,547,558 shares and 32,662,255 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	39	33
Additional paid-in capital	428,059	307,158
Accumulated deficit	(294,354)	(220,341)
Accumulated other comprehensive loss	(114)	(70)
Total stockholders' equity	133,630	86,780

Total liabilities and stockholders' equity	$190,823	$97,004

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,		
	2018	2017	2016
Revenue:			
License and milestone fees	$13,436	$530	$—
Collaborative revenue	—	313	—
Clinical compound revenue	33	68	86
Total revenue	13,469	911	86
Operating expenses:			
Research and development	75,531	48,524	49,253
General and administrative	15,320	11,872	9,233
Total operating expenses	90,851	60,396	58,486
Operating loss	(77,382)	(59,485)	(58,400)
Other income	2,980	1,156	652
Loss before benefit from income taxes	(74,402)	(58,329)	(57,748)
Benefit from income taxes	389	204	468
Net loss	$(74,013)	$(58,125)	$(57,280)
Net loss per share:			
Basic and Diluted	$(2.06)	$(1.86)	$(2.10)
Weighted average shares:			
Basic and Diluted	35,892,786	31,202,842	27,279,008
Other comprehensive income (loss), net of tax of $0:			
Change in unrealized gains (losses) on available for sale marketable securities	(44)	(73)	38
Total comprehensive loss	$(74,057)	$(58,198)	$(57,242)

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	Accumulated	Accumulated Other Comprehensive Income	Total Stockholders'
	Shares	Amount	Capital	Deficit	(Loss)	Equity
Balance at December 31, 2015	27,254,863	$ 27	$ 209,943	$ (104,891)	$ (35)	$ 105,044
Stock-based compensation expense	—	—	2,800	—	—	2,800
Shares issued upon exercise of stock options	42,000	—	123	—	—	123
Net loss	—	—	—	(57,280)	—	(57,280)
Other comprehensive income	—	—	—	—	38	38
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	5,175,000	5	92,058	—	—	92,063

of underwriting discounts and commissions and offering expenses of $6,262						
Stock-based compensation expense	—	—	7,785	—	—	7,785
Modification of equity awards	—	—	616	—	—	616
Shares issued upon vesting of performance-based 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

See Notes to Financial Statements.

Cara Therapeutics, Inc.

STATEMENTS OF CASH FLOWS

(in thousands)

	Year Ended December 31,		
	2018	2017	2016
Operating activities			
Net loss	$(74,013)	$(58,125)	$(57,280)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	9,478	5,793	2,800
Modification of equity awards	616	537	—
Depreciation & amortization	370	495	1,465
Amortization/accretion of available-for-sale marketable securities	(1,820)	(582)	(218)
Realized gain on sale of available-for-sale marketable securities	5	(5)	(23)
Realized gain on sale of property and equipment	—	(41)	—
Deferred rent costs	(156)	148	(114)
Deferred revenue	42,009	—	—
Changes in operating assets and liabilities:			
Income tax receivable	67	121	(468)
Other receivables	(803)	(36)	(7)
Prepaid expenses	(3,170)	(105)	199
Accounts payable and accrued expenses	5,116	(3,027)	6,265
Net cash used in operating activities	(22,301)	(54,827)	(47,381)
Investing activities			
Proceeds from maturities of available-for-sale marketable securities	175,300	82,156	80,380
Proceeds from sale of available-for-sale marketable securities	79,808	8,755	34,003
Purchase of available-for-sale marketable securities	(337,854)	(127,394)	(68,648)
Purchases of property and equipment	(73)	(58)	(717)
Proceeds from sale of property and equipment	—	41	—
Net cash (used in) provided by investing activities	(82,819)	(36,500)	45,018
Financing activities			
Proceeds from sale of common stock in a follow-on public offering, net of issuance costs	92,063	86,224	—
Proceeds from the sale of common stock under license agreement	14,556	—	—
Proceeds from the exercise of stock options	4,194	1,699	123
Net cash provided by financing activities	110,813	87,923	123
Net increase (decrease) in cash, cash equivalents and restricted cash	5,693	(3,404)	(2,240)
Cash, cash equivalents and restricted cash at beginning of period	10,157	13,561	15,801
Cash, cash equivalents and restricted cash at end of period	$15,850	$10,157	$13,561
Noncash financing activities			
Tenant improvements paid by landlord	$—	$—	$1,094

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 with a primary focus on pruritus as well as pain 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, including conducting preclinical studies and clinical trials of CR845/difelikefalin-based product candidates and raising capital.

As of December 31, 2018, the Company has raised aggregate net proceeds of $383,200 from several rounds of equity financing, including its initial public offering, or IPO, which closed in February 2014 and three follow-on public offerings of common stock, which closed in 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 $88,900 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, 2018, the Company had unrestricted cash and cash equivalents and marketable securities of $182,779 and an accumulated deficit of $294,354. 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 $74,013 and had net cash used in operating activities of $22,301 for the year ended December 31, 2018.

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 certain accounting standards (see Note 2, Other Accounting Pronouncements Recently Adopted: ASU 2016-18, Statement of Cash Flows (Topic 230), Restricted Cash).

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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 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 three 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, 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.

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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 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 and cash equivalents, restricted cash, accounts payable and accrued liabilities approximate their carrying values due to the short-term nature of these financial instruments. Marketable securities are reported at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by 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.

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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, municipal bonds, commercial paper and money market funds with similar underlying investments 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, 2018 or December 31, 2017.

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).

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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.

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.

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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, 2018 and 2017, the Company recorded $4,377 and $1,287 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, 2018 and December 31, 2017. 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.

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 based on their grant date fair values. The grant date fair value of stock options is estimated using the Black-Scholes option valuation model.

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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, 2018, 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.

Similarly, because the Company does not have sufficient company-specific information available to calculate the volatility of its common stock during the periods of the expected term of stock option grants (as noted above), expected volatility is based on an analysis of guideline companies, in accordance with ASC 718.

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.

On the grant date of each stock option award prior to January 1, 2017, the Company applied a forfeiture rate in order to accrue share-based compensation expense based on an estimate of the number of stock options that are expected to vest. Estimated forfeiture rates were based upon historical data of awards that were cancelled prior to vesting. The Company adjusted the total amount of compensation cost recognized for each award, in the period in which each award vested, to reflect the actual forfeitures related to that award. To the extent that the actual forfeiture rate for an award was lower than the estimated forfeiture rate, additional compensation expense was recorded in the period that the award vested. Changes in the Company's estimated forfeiture rate resulted in changes in the rate at which compensation cost for an award was recognized over its vesting period. As of January 1, 2017, the Company adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting. 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 (see Note 13, Stock-Based Compensation).

The Company accounts for options granted to non-employee consultants under ASC 505-50, Equity-Based Payments to Non-Employees. As such, the Company estimates 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 is complete, the Company revalues 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 is recognized during its vesting term. As of January 1, 2019, the Company will adopt ASU 2018-07, Compensation – Stock Compensation (Topic 718),

Improvements to Non-employee Share-Based Payment Accounting, which expands 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 will be remeasured under ASC 718 (see Note 2, Recent Accounting Pronouncements Not Yet Adopted). 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.

CARA THERAPEUTICS, INC.

NOTES TO FINANCIAL STATEMENTS

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

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, 2018, 2017 and 2016, 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

The Company recognizes rent expense for operating leases on a straight-line basis over the term of the lease, beginning on the date the Company takes possession of the property. Rent expense includes 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 determines 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 is one of the factors used to determine whether a lease is classified as operating or capital and is 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 is included in deferred rent and classified within long-term liabilities. Lease incentives made by landlords to or on behalf of the Company for leasehold improvements are recorded as deferred rent and classified as long-term liabilities. Deferred rent related to landlord incentives is amortized using the straight-line method over the lease term as an offset to rent expense. Penalties paid to landlords to terminate a lease before the contractual end date of the lease are recognized on an undiscounted basis in the Statements of Comprehensive Loss. On January 1, 2019, the Company will adopt ASU No. 2016-02, Leases (Topic 842), which amends the previous guidance for accounting and disclosure of leases (ASC 840) for both lessees and lessors. The primary effect of adoption will be the requirement to record a right-of-use asset and a corresponding lease obligation for the Stamford operating lease (see Note 2, Recent Accounting Pronouncements Not Yet Adopted).

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.

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Other Accounting Pronouncements Recently Adopted

In August 2018, the SEC adopted amendments to certain disclosure requirements in Securities Act Release No. 33-10532, Disclosure Update and Simplification. These amendments eliminate, modify, or integrate into other SEC requirements certain disclosure rules. Among the amendments is the requirement to present an analysis of changes in stockholders' equity in the interim financial statements included in quarterly reports on Form 10-Q. The analysis, which can be presented as a footnote or separate statement, is required for the current and comparative quarter and year-to-date interim periods. The amendments are effective for all filings made on or after November 5, 2018. In light of the anticipated timing of effectiveness of the amendments and expected proximity of effectiveness to the filing date for most filers' quarterly reports, the SEC's Division of Corporate Finance issued a Compliance and Disclosure Interpretation related to Exchange Act Forms, or CDI – Question 105.09, that provides transition guidance related to this disclosure requirement. CDI – Question 105.09 states that the SEC would not object if the filer's first presentation of the changes in stockholders' equity is included in its Form 10-Q for the quarter that begins after the effective date of the amendments. As such, the Company adopted these SEC amendments on November 5, 2018 and will present the analysis of changes in stockholders' equity in its interim financial statements in the Company's Quarterly Report on Form 10-Q for the quarter ending March 31, 2019. The adoption of these SEC amendments will not have a material effect on the Company's financial position, results of operations, cash flows or stockholders' equity.

As of January 1, 2018, the Company adopted ASU No. 2017-09, Compensation – Stock Compensation (Topic 718) - Scope of Modification Accounting, or ASU 2017-09, which clarifies that a change to the terms or conditions of a share-based payment award should be accounted for as a modification only if the fair value, vesting conditions or classification (as equity or liability) of the award changes as a result of the change in terms or conditions. Modification of a share-based payment award may result in the Company recognizing additional compensation expense. The Company does not expect to frequently modify, the fair value, vesting conditions or classification of its share-based payment awards. The Company does not expect this guidance to have a material effect on its financial position, results of operations or cash flows. However, if and when modifications occur, their effect could be material to the Company's financial position, results of operations or cash flows.

As of January 1, 2018, the Company adopted ASU No. 2017-01, Business Combinations (Topic 805), Clarifying the Definition of a Business, or ASU 2017-01, that clarifies the definition of a business to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. ASU 2017-01 requires an entity to evaluate if substantially all of the fair value of the gross assets acquired or disposed of is concentrated in a single identifiable asset or a group of similar identifiable assets; if so, the set of transferred assets and activities is not a business. ASU 2017-01 also requires a business to include at least an input and one substantive process that together significantly contribute to the ability to create output and removes the evaluation of whether a market participant could replace missing elements. The adoption of ASU 2017-01 did not have a material effect on the Company's financial position, results of operations or cash flows.

As of January 1, 2018, the Company adopted ASU No. 2016-18, Statement of Cash Flows (Topic 230), Restricted Cash (a consensus of the Emerging Issues Task Force), or ASU 2016-18, which changes the presentation of the cash flow statement to include amounts generally described as restricted cash or restricted cash equivalents, together with cash and cash equivalents, when reconciling the beginning-of-period and end-of-period amounts shown on the statement of cash flows. ASU 2016-18 also requires additional disclosures concerning the nature of the restrictions on

cash and cash equivalents and a reconciliation between amounts of cash, cash equivalents and restricted cash on the balance sheet and statement of cash flows for each period presented. Upon adoption, ASU 2016-18 was applied retrospectively to all periods presented. The Company historically presented changes in restricted cash as an investing activity in the statement of cash flows. Upon adoption of ASU 2016-18, such changes are reflected in the beginning and ending balances of cash, cash equivalents and restricted cash for all periods presented (see Note 7, Restricted Cash).

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Recent Accounting Pronouncements Not Yet Adopted

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 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 does not expect that the adoption of ASU 2018-13 will have a material effect on its results of operations, financial position, cash flows or footnote disclosures.

In June 2018, the FASB issued ASU No. 2018-07, Compensation—Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting, or ASU 2018-07, which expands the scope of Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees. ASU 2018-07 applies to all share-based payment transactions in which a grantor acquires goods or services to be used or consumed in a grantor's own operations by issuing share-based payment awards. Accordingly, under ASU 2018-07, the fair value of stock options granted to nonemployees will be measured only on the grant date, the amount of which will be recognized as compensation expense over the nonemployee's service (vesting) period in the same period(s) and in the same manner as if the Company had paid cash for the goods or services instead of paying with or using share-based payment awards. On an award-by-award basis, the Company may elect to use the contractual term as the expected term when

estimating the fair value of a nonemployee award to satisfy the measurement objective. Prior guidance under Subtopic 505-50 required the fair value of nonemployee stock options to be marked to market at each reporting period during the service period, which resulted in volatility of compensation expense during that period. ASU 2018-07 is effective for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. Early adoption is permitted, but no earlier than an entity's adoption date of Topic 606. The Company will adopt ASU 2018-07 on January 1, 2019 on a modified retrospective basis and will remeasure, on that date, the fair value of all outstanding unvested stock options that had been granted to nonemployees. The Company expects that the adoption of ASU 2018-07 will not have a material effect on its results of operations, financial position or cash flows because grants of stock options to nonemployees have been insignificant.

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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. ASU 2016-13 will be effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. As such, the Company expects to adopt ASU 2016-13 on January 1, 2020 and is currently evaluating the effect it will have on its results of operations, financial position and cash flows.

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), or ASU 2016-02, which amends the current guidance for the accounting and disclosure of leases (ASC 840) for both lessees and lessors. The Company has completed its review of existing contracts and has identified one material contract that contains a lease. The primary effect of adoption will be the requirement to record a right-of-use asset and a corresponding lease obligation for the Stamford operating lease (see Note 17, Commitments and Contingencies). ASU 2016-02 is effective for interim and annual periods beginning after December 31, 2018 but may be adopted earlier. ASU 2016-02 requires modified retrospective adoption. However, the FASB issued ASU 2018-11, Leases (Topic 842): Targeted Improvements, or ASU 2018-11, which allows entities to elect an optional transition method by continuing to apply the guidance in ASC 840, including its disclosure requirements, in the comparative periods presented in the year that they adopt the new leases guidance in ASC 842. Entities that elect this optional transition method would record the cumulative effect of adoption on the effective date rather than at the beginning of the earliest comparative period presented. The Company will adopt ASU 2016-02 and ASU 2018-11 on January 1, 2019 using the optional transition method from ASU 2018-11. The Company expects that the adoption of ASU 2016-02 or ASU 2018-11 will not have a material impact on its Statements of Comprehensive Loss or its Statements of Cash Flows, but it expects that the lease liability recorded on the Balance Sheet beginning on January 1, 2019 will be between $5,000 and $6,000.

3. Available-for-Sale Marketable Securities

As of December 31, 2018, and 2017, the Company's available-for-sale marketable securities consisted of debt securities issued by U.S. government-sponsored entities and by investment grade institutions. As of December 31, 2018, the Company's available-for-sale marketable securities also included debt securities issued by the U.S. Treasury and municipal bonds. As of December 31, 2017, the Company's available-for-sale securities also included a money market fund.

The following tables summarize the Company's available-for-sale marketable securities by major type of security as of December 31, 2018, and 2017:

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

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As of December 31, 2017

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market funds	$ 39,988	$ —	$ (37)	$ 39,951
U.S. government agency obligations	7,799	—	(5)	7,794
Corporate bonds	15,919	—	(12)	15,907
Commercial paper	19,545	—	(16)	19,529
Total available-for-sale marketable securities	$ 83,251	$ —	$ (70)	$ 83,181

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, 2018, the Company's marketable debt securities mature at various dates through November 2020. The amortized cost and fair values of marketable debt securities by contractual maturity were as follows. The table does not include money market funds that are classified as available-for sale marketable securities as of December 31, 2017.

Contractual maturity	As of December 31, 2018		2017	
	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Less than one year	$ 146,363	$ 146,302	$ 43,263	$ 43,230
One year to two years	21,449	21,396	—	—
Total	$ 167,812	$ 167,698	$ 43,263	$ 43,230

During the years ended December 31, 2018 and 2017, the Company sold shares of its investments in available-for-sale marketable securities with total fair values of $79,808 and $8,755, respectively. 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 each year resulted in realized (losses) gains, totaling $(5) and $5, respectively.

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	
As of December 31, 2018	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)

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	Less than 12 Months		12 Months or Greater		Total	
As of December 31, 2017	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses
Money market funds	$39,951	$ (37)	$ —	$ —	$39,951	$ (37)
U.S. government agency obligations	7,794	(5)	—	—	7,794	(5)
Corporate bonds	15,907	(12)	—	—	15,907	(12)
Commercial paper	19,031	(16)	—	—	19,031	(16)
Total	$82,683	$ (70)	$ —	$ —	$82,683	$ (70)

As of December 31, 2018, and 2017, the Company held a total of 69 out of 84 positions and 30 out of 31 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, 2018, or 2017. 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.

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, 2018, 2017 and 2016.

	Total Accumulated Other Comprehensive Income (Loss)
Balance, December 31, 2015	$ (35)
Other comprehensive income before reclassifications	61
Amount reclassified from accumulated other comprehensive income	(23)
Net current period other comprehensive income	38
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)

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

Component of AOCI	Year Ended December 31, 2018	2017	2016	Affected Line Item in the Statements of Comprehensive Loss
Unrealized gains (losses) on available-for-sale marketable securities				
Realized (losses) gains on sale of securities	$(5)	$ 5	$ 23	Other income
	—	—	—	Income tax benefit
	$(5)	$ 5	$ 23	

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

5. Prepaid Expenses

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. As of December 31, 2017, the amount of prepaid expenses was $1,635, consisting of $1,287 of prepaid R&D clinical costs, $124 of prepaid insurance and $224 of other costs.

6. Property and Equipment, Net

Property and equipment, net consists of the following:

	December 31,	
	2018	2017
Computer and office equipment	$211	$158
Laboratory equipment	628	628
Furniture and fixtures	47	27
Leasehold improvements	1,128	1,128
	$2,014	$1,941
Less accumulated depreciation and amortization	1,134	764
Property and equipment, net	$880	$1,177

Depreciation and amortization expense included in R&D expense and General and administrative expense was $370, $495 and $1,465 for the years ended December 31, 2018, 2017 and 2016, respectively.

In connection with the Company’s relocation of its operating facility from Shelton, Connecticut to Stamford, Connecticut, the Company accelerated the amortization of the Shelton leasehold improvements during the period from December 2015 (signing of the Stamford lease) to May 2016 (the date that the Shelton facility was vacated) (see Note 17, Commitments and Contingencies). In addition, during the years ended December 31, 2017 and 2016, the Company wrote-off $7,816 and $397, respectively, of fully-depreciated Shelton property and equipment, including leasehold improvements, that was not re-located to the Stamford headquarters. 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). 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, 2018, 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 is required to remain at $769 through May 2019 and may, upon request from the Company, thereafter 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 is contingent upon the Company not being in default of any provisions of that lease prior to request for the reduction. As of December 31, 2018, the Company had $361 of restricted cash related to the Shelton lease in current assets and $408 in long-term assets. As of December 31, 2017, the Company had $769 of restricted cash related to the Stamford lease in long-term assets.

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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,	
	2018	2017
Cash and cash equivalents	$15,081	$9,388
Restricted cash, current assets	361	—
Restricted cash, long-term assets	408	769
Total cash, cash equivalents, and restricted cash shown in the Statements of Cash Flows	$15,850	$10,157

8. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	December 31,	
	2018	2017
Accounts payable	$4,371	$3,829
Accrued research projects	6,079	2,356
Accrued professional fees	802	384
Accrued compensation and benefits	2,370	1,864
Accrued other	—	73
	$13,622	$8,506

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, 2018, there were 39,547,558 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.

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 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.

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).

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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.

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).

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, 2018 and 2017 and by level within the fair value hierarchy:

Fair value measurement as of December 31, 2018:

Financial assets 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	$ —

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Fair value measurement as of December 31, 2017:

Financial assets 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 fund and checking accounts	$9,388	$ 9,388	$ —	$ —
Available-for-sale marketable securities:				
Money market fund	39,951	—	39,951	—
U.S. government agency obligations	7,794	—	7,794	—
Corporate bonds	15,907	—	15,907	—
Commercial paper	19,529	—	19,529	—
Restricted cash:				
Commercial money market account	769	769	—	—
Total financial assets	$93,338	$ 10,157	$ 83,181	$ —

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, 2018, 2017 and 2016. There were no transfers of financial assets between Levels 1, 2, or 3 classifications during the years ended December 31, 2018, 2017 and 2016.

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.

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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).

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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 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, 2018, 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.

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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, 2018, 2017 and 2016, the Company recognized clinical compound revenue of $33, $68 and $86, respectively, from the sale of clinical compound to Maruishi.

The Company incurred R&D expense related to the Maruishi Agreement of $30, $61 and $78 (all related to the cost of clinical compound sold to Maruishi) during the years ended December 31, 2018, 2017 and 2016, 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.

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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, 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. As of December 31, 2017, the Company had no balances of receivables, other assets or deferred revenue related to the Maruishi and CKDP Agreements.

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.

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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, 2018, $13,436 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, 2018, 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.

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).

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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.

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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. 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 $42,009 at December 31, 2018 will be recognized by 2020, as the R&D services are performed, subject to certain development and regulatory uncertainties.

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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, 2018, 2017 and 2016, 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.

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.

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13. Stock-Based Compensation

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.

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, 2019, the aggregate number of shares of common stock that may be issued pursuant to Stock Awards under the 2014 Plan automatically increased from 4,900,481 to 6,086,907. 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 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.

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.

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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. Such grants are accounted for pursuant to ASC 505-50, Equity-Based Payments to Non-Employees (refer to Note 2, Summary of Significant Accounting Policies - Stock-Based Compensation).

A summary of the Company's stock option activity related to employees, non-employee members of the Board of Directors and non-employee consultants as of and for the year ended December 31, 2018 is as follows:

	Number of Options	Weighted-Average Exercise Price	Aggregate Intrinsic Value
Outstanding at December 31, 2017	3,492,141	$ 11.75	
Granted	1,197,500	16.15	
Exercised	(451,685)	9.29	
Expired	(60,111)	10.79	
Forfeited	(173,423)	12.12	
Outstanding at December 31, 2018	4,004,422	$ 13.34	$ 6,627
Weighted average remaining contractual life as of December 31, 2018 (in years)	7.92		
Options exercisable at December 31, 2018	1,974,979	$ 11.70	$ 4,985
Weighted average remaining contractual life as of December 31, 2018 (in years)	7.00		
Options vested and expected to vest as of December 31, 2018	4,004,422	$ 13.34	$ 6,627
Weighted average remaining contractual life as of December 31, 2018 (in years)	7.92		

The total fair value of options vested during the years ended December 31, 2018, 2017 and 2016 was $9,023, $5,303 and $3,589, respectively. The intrinsic value of options exercised during the years ended December 31, 2018, 2017 and 2016 was $3,893, $2,285 and $126, respectively.

During the years ended December 31, 2018, 2017 and 2016, the Company granted 1,197,500, 1,328,500 and 1,078,000 stock options, respectively, to employees, non-employee members of the Board of Directors or non-employee consultants. The fair values of the stock options granted to those groups were 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,		
	2018	2017	2016
Risk-free interest rate	2.51% - 3.09%	1.85% - 2.57%	1.19% - 1.93%
Expected volatility	82.6% - 92.3%	83.3% - 84.5%	67.8% - 77.8%
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	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, 2018, 2017 and 2016 was $11.99, $11.46 and $4.28, respectively.

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At the end of each fiscal quarter during the years ended December 31, 2018, 2017 and 2016, the Company used the Black-Scholes option valuation model with the following ranges of assumptions 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:

	Year Ended December 31,		
	2018	2017	2016
Risk-free interest rate	1.82% - 3.02%	1.28% - 2.39%	1.35% - 2.38%
Expected volatility	58.2% - 101.0%	74.6% - 87.3%	70.8% - 75.5%
Expected dividend yield	0%	0%	0%
Expected life of non-employee options (in years)	0.25 - 8.94	0.62 - 9.94	7.08 - 9.60

Under ASC 505-50, upon re-measurement of each award, income or expense is recognized during its vesting term (see Note 2, Accounting Pronouncements Not Yet Adopted for the adoption of ASU 2018-07 on January 1, 2019).

The weighted average fair value of outstanding options that had been granted to nonemployee consultants, as re-measured during the vesting period of each tranche in accordance with ASC 505-50 during the years ended December 31, 2018, 2017 and 2016 was $8.74, $10.16 and $4.81, respectively.

On January 1, 2017, the Company adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting (see Note 2, Basis of Presentation - Recently Adopted Accounting Pronouncements). 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 for all stock option awards that were unvested as of that date.

During the years ended December 31, 2018, 2017 and 2016, the Company recognized compensation expense relating to stock options (excluding compensation expense related to the vesting of restricted stock units of $476 in R&D and $1,217 in G&A in 2018), as follows:

	Year Ended December 31,		
	2018	2017	2016
Research and development	$3,919	$2,433	$1,301
General and administrative	4,482	3,897	1,499
Total stock option expense	$8,401	$6,330	$2,800

Included in the table above are the following amounts of compensation expense recognized with regard to stock options that were granted to non-employee consultants, including the effect of re-measurement of the fair values of those options, as described above:

	Year Ended December 31,		
	2018	2017	2016
Research and development	$195	$170	$(79)
General and administrative	192	200	(20)
Total stock option expense	$387	$370	$(99)

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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 will 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 will provide 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 will continue to vest under their original vesting conditions as long as he provides continuous service to the Company (including as a consultant). The term of his consulting agreement is through July 22, 2019, if not terminated earlier per the terms of the consulting agreement or extended by the Company.

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, 2018, 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 $20,474, which is expected to be realized over a weighted average period of 2.84 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, 2018, 2017 and 2016.

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14. Income Taxes

The Company's benefit from income taxes is as follows:

	December 31,		
	2018	2017	2016
Current:			
Federal	$—	$—	$—
State	(389)	(204)	(468)
	(389)	(204)	(468)
Deferred:			
Federal	—	—	—
State	—	—	—
	—	—	—
Benefit from income taxes	$(389)	$(204)	$(468)

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,		
	2018	2017	2016
Income taxes using U.S. federal statutory rate	21.00 %	34.00 %	34.00 %
State income taxes, net of federal benefit	6.82 %	5.33 %	5.44 %
Tax Cuts and Jobs Act	0.00 %	-44.43 %	0.00 %
Impact of R&D tax credit on effective tax rate	3.48 %	3.25 %	3.24 %
Stock option shortfalls and cancellations	-0.43 %	0.21 %	-0.07 %
Permanent items and other	-0.15 %	-0.56 %	-0.64 %
Change in valuation allowance	-31.76 %	2.55 %	-41.17 %
Provision to return	0.03 %	0.00 %	0.00 %
Non-taxable revenue	1.54 %	0.00 %	0.00 %
	0.53 %	0.35 %	0.80 %

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

	December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$73,578	$54,831
Federal and state tax credits	11,108	8,401
Deferred revenue	1,111	—
Stock-based compensation expense	3,605	2,382
Other	420	582
	89,822	66,196
Deferred tax liabilities:		
Accelerated depreciation	(7)	(23)
Valuation allowance	(89,815)	(66,173)
Net deferred tax asset	$—	$—

A 100% valuation allowance has been recorded on the deferred tax asset as of December 31, 2018 and 2017 because management believes it is more likely than not that the asset will not be realized. The change in the valuation allowance during 2018 and 2017 was $23,642 and $618, respectively.

In 2017, the Company recorded a cumulative-effect adjustment for the tax benefit of approximately $840 related to the exercise of non-qualified stock options and the disqualified disposition of incentive stock options. As a result of the adoption of ASU 2016-09 on January 1, 2017, the tax benefit related to the exercise of stock options was recognized as a deferred tax asset with a corresponding cumulative adjustment to retained earnings, that is offset by a valuation allowance against retained earnings.

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. As of December 31, 2018 and 2017, 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.

The Company files income tax returns in the United States and the State of Connecticut. All tax years since the date of the Company's incorporation remain open to examination by the major taxing jurisdictions (state and federal) to which the Company is subject, as carry-forward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service, or IRS, or other authorities if they have or will be used in a future period. The Company is not currently under examination by the IRS, or any other jurisdictions, for any tax year.

At December 31, 2018, the Company had federal and state net operating loss carryforwards of approximately $274,764 and $267,973, 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 approximately $9,925 and $1,236, 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 2018 remain open to U.S. federal and state tax examinations.

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On December 22, 2017, the United States enacted the Tax Cuts and Jobs Act (the "Act"). The Act, 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. During the year ended December 31, 2017, the Company reduced deferred tax assets by $25,913, offset by a corresponding reduction to its valuation allowance, as a result of the re-measurement of deferred tax assets and liabilities from its 34% effective rate under existing law to the new lower statutory rate of 21%. As of December 31, 2018 and 2017, the Company did not have any foreign subsidiaries and the international aspects of the Act were not applicable.

On December, 22, 2017, SAB 118 was issued due to the complexities involved in accounting for the recently enacted Tax Act. SAB 118 requires the Company to include in its financial statements a reasonable estimate of the impact of the Tax Act on earnings to the extent such estimate has been determined. Accordingly, the U.S. provision for income tax for 2017 was based on the reasonable estimate guidance provided by SAB 118. The Company has finalized its accounting for the Act as of December 31, 2018, which resulted in insignificant adjustments.

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,		
	2018	2017	2016
Basic:			
Weighted average shares outstanding	35,892,786	31,202,842	27,279,008
Diluted:			
Weighted average shares outstanding - Basic	35,892,786	31,202,842	27,279,008
Common stock options *	—	—	—
Denominator for diluted net loss per share	35,892,786	31,202,842	27,279,008

*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,

	2018	2017	2016
Net loss	$(74,013)	$(58,125)	$(57,280)
Weighted-average common shares outstanding:			
Basic and Diluted	35,892,786	31,202,842	27,279,008
Net loss per share:			
Basic and Diluted	$(2.06)	$(1.86)	$(2.10)

As of December 31, 2018, 2017 and 2016, 4,004,422, 3,492,141 and 2,548,408 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.

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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, 2018, 2017 and 2016, employer contributions to the plan were $198, $174 and $118, respectively.

17. Commitments and Contingencies

Contractual obligations and commitments as of December 31, 2018, comprising future minimum lease payments under the Company's Stamford lease, were as follows:

	Payment Due for the Year Ending December 31,					
	2019	2020	2021	2022	2023	Total
Stamford operating lease	$1,215	$1,240	$1,264	$1,288	$1,164	$6,171

Stamford Operating Lease

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. 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. The Company records monthly rent expense on a straight-line basis from March 2016, upon taking possession of the Premises, through November 2023. As of December 31, 2018 and 2017, the balance of deferred lease obligation, representing the difference between cash rent paid and straight-line rent expense, was $864 and $876, respectively. The Stamford Lease is renewable for one five-year term.

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. The portion of Deferred lease obligation that is related to tenant improvements is being amortized as a reduction to rent expense over the same term as rent expense. As of December 31, 2018 and 2017, the balance of Deferred lease obligation related to tenant improvements was $698 and $842, respectively.

Total rent expense under the Stamford Lease was $974, $935 and $797 for the years ended December 31, 2018, 2017 and 2016, respectively.

In connection with the signing of the Stamford Lease, the Company entered into a standby letter of credit agreement for $769, 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).

Shelton Operating Lease

In May 2016, the Company relocated its headquarters to Stamford, Connecticut and vacated its former operating facility in Shelton, Connecticut, which the Company continued to lease under an operating lease, or the Shelton Lease. The Shelton Lease terminated in November 2017.

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The Shelton Lease, as amended, required monthly lease payments through its term. The Company recorded monthly rent expense associated with the Shelton Lease on a straight-line basis from inception of the lease in October 2007 through May 2016, when the facility was vacated. In accordance with the accounting guidance in ASC 420-10-25-13 regarding exit or disposal cost obligations, as of May 2016, the Company recorded rent expense, within R&D expense and General and administrative expense, and accrued a liability of $1,312, which represented the fair value of costs that continued to be incurred during the remaining term of the Shelton Lease without economic benefit to the Company.

Total rent expense under the Shelton Lease was $1,127 for the year ended December 31, 2016.

In conjunction with the signing of the Shelton Lease, the Company entered into a standby letter of credit agreement, which expired on December 13, 2017, as a security deposit for the premises. The balance of the letter of credit was $700, which was secured with restricted cash.

The Company accelerated the amortization of the Shelton leasehold improvements from the date of signing of the Stamford lease in December 2015 through the date that the Company vacated the Shelton facility in May 2016. Additional amortization expense as a result of such acceleration amounted to $899 (additional net loss per share of $0.03) for the year ended December 31, 2016.

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, 2018 and 2017. 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, 2018 and 2017. The operating results for any period are not necessarily indicative of results for any future periods.

	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)

	Year Ended December 31, 2017			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$911	$—	$—	$—
Net loss - Basic and Diluted	(22,204)	(9,300)	(12,444)	(14,177)
Loss per share - Basic and Diluted	$(0.81)	$(0.29)	$(0.38)	$(0.43)(a)

(a) The difference between the sum of net loss per share, basic and diluted, as calculated on a quarterly basis for 2017 ($1.91), and net loss per share, basic and diluted, for the year ended December 31, 2017 ($1.86) is due to the denominator used for the year ended December 31, 2017, which weights shares outstanding on a cumulative basis and reflects the issuance of 5.1 million shares of the Company's common stock during the year ended December 31, 2017 (see Note 9, Stockholders' Equity).