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, 2017

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

Indicate by check mark 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 $405,378,264. For purposes of this calculation, shares of common stock held by directors and officers and their affiliated entities at June 30, 2017 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 8, 2018 was 32,690,236.

Documents Incorporated By Reference

Portions of the registrant's Proxy Statement for its 2018 Annual Meeting of Stockholders, to be filed with the Securities and Exchange Commission no later than 120 days after December 31, 2017, are incorporated by reference in Part III of this Annual Report on Form 10-K.

CARA THERAPEUTICS, INC.
2017 ANNUAL REPORT ON FORM 10-K

TABLE OF CONTENTS

		PAGE
	PART I	
Item 1.	Business	2
Item 1A.	Risk Factors	31
Item 1B.	Unresolved Staff Comments	69
Item 2.	Properties	69
Item 3.	Legal Proceedings	69
Item 4.	Mine Safety Disclosures	69
	PART II	
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	70
Item 6.	Selected Financial Data	72
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	74
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	91
Item 8.	Financial Statements and Supplementary Data	91
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	91
Item 9A.	Controls and Procedures	92
Item 9B.	Other Information	92
	PART III	
Item 10.	Directors, Executive Officers and Corporate Governance	93
Item 11.	Executive Compensation	93
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	93
Item 13.	Certain Relationships and Related Transactions, and Director Independence	93
Item 14.	Principal Accounting Fees and Services	93
	PART IV	
Item 15.	Exhibits, Financial Statement Schedules	94

PART I

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

Cautionary Note Regarding Forward-Looking Statements

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

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

- the success and timing of our clinical trials, including our clinical trial programs for CR845/difelikefalin injection in acute post-operative pain, 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 uremic pruritus;
- 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 pain management, including the postoperative and chronic pain 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, including Maruishi Pharmaceuticals Co. Ltd., or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or CKDP, 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 designed to alleviate pruritus and pain by selectively targeting kappa opioid receptors. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), that target the body's peripheral nervous system and certain immune cells. The U.S. Food and Drug Administration, or FDA, has conditionally accepted KORSUVA as the trade name for CR845/difelikefalin injection, an investigational drug product for the treatment of itch, whose safety and efficacy have not been fully evaluated by any regulatory authority. In Phase 2 trials, KORSUVA (CR845/difelikefalin) has demonstrated statistically significant reductions in itch intensity and concomitant improvement in quality of life measures in hemodialysis patients with moderate-to-

severe chronic kidney disease-associated pruritus, or CKD-aP, and is currently being investigated in Phase 3 trials in hemodialysis patients with CKD-aP. In addition, CR845/difelikefalin has also demonstrated initial signs of efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics.

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.

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 and dialysis 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 appears to be no need for a centrally-acting kappa opioid to modulate itch signals. 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 unselective 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 the following categories on the basis of the underlying causative disease: renal or uremic pruritus, cholestatic pruritus, dermatological pruritus, hematologic pruritus, endocrine pruritus, pruritus related to malignancy and idiopathic generalized pruritus. According to a study Cara conducted with IMS Health (now IQVIA) utilizing medical claims data from 2013, nearly 45 million patients have been diagnosed with diseases known to trigger pruritus in the United States alone. Of those patients, nearly half (47%), or 21 million, 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 (Elidel, Protopic) or gabapentin.

Chronic Kidney Disease-Associated Pruritus (CKD-aP)

CKD-aP (also known as uremic pruritus) can occur in patients with chronic renal failure and is most often 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 million patients globally undergoing dialysis in

2016. It is estimated that nearly 70% of these patients suffer from some renal or uremic pruritus with over 50% of these patients experiencing moderate to severe pruritus according to a study of dialysis patients.

Currently, there are no approved products in the United States 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. Nalfurafine is a kappa opioid receptor agonist, but it also has partial mu-opioid receptor activity. Mu agonists, like morphine, are known to cause itch. Kappa agonists that cross the blood brain barrier, like nalfurafine, are also known to cause CNS-related adverse events resulting in high rates of discontinuation. The limited efficacy in light of concerns about adverse events caused European Medicines Agency not to approve nalfurafine for the treatment of uremic pruritus in 2013.

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 patients suffer from some level of pruritus in the United States. Many of these patients are sub-optimally treated for their pruritus with products not approved to treat their condition.

The Market Opportunity – Pain 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. 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 a recent 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 severity of pain is the key factor in determining the appropriate therapy. Mild or mild-to-moderate pain is generally treated with non-opioid products, such as oral formulations of nonsteroidal anti-inflammatory drugs, or NSAIDs (e.g., ibuprofen, naproxen), aspirin, and acetaminophen. Moderate-to-severe pain, on the other hand, is typically treated with products containing traditional mu opioids. Mu opioid analgesics are effective to some degree for many patients, but have poor side effect and abuse liability profiles, which limits or precludes their use in treating less severe pain. For many people with moderate-to-severe pain, opioid analgesics are the only effective method of treating pain. As a result, these opioid analgesics are among the largest prescription drug classes in the United States. According to IQVIA, the total U.S. market for pain management pharmaceuticals was $45.5 billion in 2017. The prescription pain management market in the United States is dominated by opioid analgesics, which, according to IQVIA data, represented 53% of the 406 million analgesic prescriptions written in 2017 and accounted for sales of $6.9 billion in that year. In 2016, according to Visiongain, an independent industry research company, total sales for pain therapies worldwide, exceeded $67.8 billion.

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 central nervous system, or 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.

Postoperative Pain Market

Postoperative pain represents a substantial part of the overall 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. Moderate-to-severe pain in a hospital or other medical setting is most often treated

with injectable analgesics. The United States I.V./injectable analgesic therapy market primarily consists of mu opioid agonists, such as morphine, hydromorphone and fentanyl, and certain non-opioid analgesics, such as Toradol® (and related generic I.V. ketorolac products), Caldolor® (I.V. ibuprofen), Dyloject® (I.V. diclofenac sodium) and Ofirmev® (I.V. acetaminophen). In 2014, there were 234.3 million doses of injectable opioid analgesics used in United States according to the IMS Health (now IQVIA) NSP Audit.

According to Practice Guidelines developed by the American Society of Anesthesiologists, the standard of care for treating acute postoperative pain is multimodal analgesia, which includes the administration of two or more drugs that act by different mechanisms for providing analgesia in a manner that will minimize the occurrence of adverse events. When patients are ready for discharge, a transition is typically made to a prescription oral pain medication, allowing patients to self-administer relatively strong analgesics after being discharged home. This transition from an I.V. pain medication to an oral pain medication is commonly referred to as I.V.-to-oral transition, or "step-down" therapy.

Strong mu opioid analgesics, such as morphine, fentanyl, and hydromorphone, are mainstays of pain treatment in the immediate postoperative period and are used as part of a multimodal analgesic approach. However, the use of strong mu opioid analgesics is associated with an array of unwanted and serious side effects, including postoperative opioid-induced respiratory depression, or POIRD, postoperative nausea and vomiting, or PONV, and opioid-induced bowel dysfunction, which contributes to the severity of postoperative ileus. According to Anesthesiology News, a trade journal, the incidence of POIRD may be as high as 29%, can occur unexpectedly in even the healthiest of patients, and exerts a disproportionately high toll on length of stay and hospital costs due to the significant expenses associated with the treatment of POIRD. According to an article published in Best Practice & Research Clinical Anaesthesiology, a trade journal, PONV occurs in approximately one-third of surgical patients overall and is one of the most important factors in determining length of stay after surgery, resulting in estimated annual costs in the U.S. in the range of $1 billion. These mu opioid-related adverse events not only significantly increase the cost of care, but also reduce a patient's quality of care and lead to sub-optimal recovery.

Nonopioid analgesics formulated for injection or infusion, including I.V. acetaminophen and NSAIDs, such as I.V. ibuprofen, are available as alternatives to mu opioids to relieve acute pain, but their use is limited in a postoperative care setting as a result of their limited efficacy. I.V. acetaminophen and NSAIDs also have side effects that limit their use at higher, more efficacious doses. Acetaminophen is associated with risk of liver toxicity, which can be fatal, and NSAIDs are associated with risks of bleeding, serious gastrointestinal side effects including ulcers, kidney damage, and serious cardiovascular thrombotic events such as stroke and heart attack, which can be fatal.

Chronic Pain Market

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. 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.

On April 7, 2005, the FDA announced a decision to require boxed warnings of potential cardiovascular risk for all NSAIDs. The 2005 FDA warning related to cardiovascular adverse events associated with NSAIDs and the increased awareness of the risk of liver toxicity associated with high doses of acetaminophen have led to increased use of mu opioid analgesics for the treatment of chronic pain. However, the use of mu opioid analgesics carries significant additional risks. Chronic opioid use causes patients to develop tolerance for the opioid, which results in the patient needing increasing opioid doses to achieve the same level of pain relief. For the most commonly prescribed analgesic combination products, the need for increasing doses to achieve the same level of pain relief means exposure to increasing amounts of NSAIDs or acetaminophen, which carry the risks attendant to these therapeutics. Moreover, due to their CNS activity, mu opioids produce feelings of euphoria, which can give rise to

abuse and addiction. Underlining the severity of this issue, in September 2013, the FDA announced class-wide safety labeling changes and new post-market study requirements for all extended-release and long-acting mu opioid analgesics intended to treat pain. In support of this action, the FDA Commissioner stated that "[t]he FDA is invoking its authority to require safety labeling changes and post-market studies to combat the crisis of misuse, abuse, addiction, overdose, and death from these potent drugs that have harmed too many patients and devastated too many families and communities." In addition, as a result of their potential for misuse, abuse and addiction, currently approved mu opioids are strictly regulated by the DEA under the Controlled Substances Act, which imposes strict registration, record keeping and reporting requirements, security control and restrictions on prescriptions, all of which significantly increase the costs and the liability attendant to prescription opioid analgesics.

The Unmet Need in Pain Management

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 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.

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 of KORSUVA (CR845/difelikefalin) injection in hemodialysis, or HD, patients suffering from moderate to severe CKD-aP. We also expect to initiate an international Phase 3 study with KORSUVA (CR845/difelikefalin) injection in multiple countries later this year. 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 data from a Phase 2/3 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 improvement 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 and expect to seek one or more global development and commercialization partner(s). We already have development and commercialization agreements with Maruishi and with 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 (CLD-aP) and certain dermatologic conditions. Based on potent anti-pruritic (anti-itch) 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 Phase 1 safety and pharmacokinetic, or PK, studies with Oral KORSUVA (CR845/difelikefalin) in different patient populations where pruritus continues to be a major unmet medical need. In the fourth quarter of 2017, we initiated a Phase 1 study with Oral KORSUVA (CR845/difelikefalin) in patients with CKD to determine drug exposure to inform dose selection for a Phase 2 study in patients with CKD-aP, which we expect to initiate in the first half of 2018. We are also conducting 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.

Continue to advance I.V. CR845/difelikefalin for the treatment of moderate-to-severe acute pain in acute care settings in the United States. We are conducting an adaptive Phase 3 trial of I.V. CR845/difelikefalin for postoperative pain. An interim conditional power analysis of our adaptive Phase 3 trial of I.V. CR845/difelikefalin for postoperative pain was conducted in the second quarter of 2017 and the study continues to test two doses of I.V. CR845/difelikefalin (0.5 ug/kg and 1 ug/kg). Based on guidance from the FDA, we believe we will require at least 500 total exposures to CR845/difelikefalin at the highest to-be-marketed dose, including all Phase 1, Phase 2 and Phase 3 trials, prior to submitting a new drug application, or NDA, to the FDA for this indication.

Build a sales and marketing organization to commercialize I.V. CR845/difelikefalin for acute pain in the acute care setting in the United States, if approved. We are planning to establish a hospital-based sales force to market I.V. CR845/difelikefalin to physicians in the United States, if approved. We believe that a sales force of approximately 80 sales professionals will be able to reach a large majority of our target market. We also intend to build a medical liaison organization as well as a reimbursement infrastructure to support our sales and marketing efforts.

Establish partnerships for further development and commercialization of CR845/difelikefalin for chronic pain indications. We do not intend to further develop and commercialize Oral CR845/difelikefalin on our own and will 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 product candidate, CR845/difelikefalin, is a new chemical entity, which is designed to selectively stimulate kappa, rather than mu, 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, or nerves outside of the brain and spinal cord. 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 acute psychiatric disorders. CR845/difelikefalin specifically targets 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 signals peripherally without any significant activation of mu or kappa opioid receptors in the CNS, it is generally not expected to produce the CNS-related side effects of mu opioids or the psychiatric side effects

associated with centrally-active kappa opioids. CR845/difelikefalin has been administered to more than 1,800 human subjects in Phase 1, Phase 2, Phase 2/3 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 well tolerated in these clinical trials.

Based on the clinical trials and preclinical studies we have completed to date, we believe that CR845/difelikefalin, if approved, will be attractive to both patients and physicians as a treatment for moderate-to-severe pain and pruritus associated with certain diseases such as Chronic Kidney Disease-associated pruritus, or CKD-aP, Chronic Liver Disease associated pruritus, or CLD-aP and others due to the following attributes:

- novel, peripherally-acting, kappa opioid receptor agonist mechanism of action;
- evidence of efficacy in completed clinical trials of pain and pruritus;
- potential for reducing mu opioid use and opioid-related adverse events, or AEs, such as nausea and vomiting;
- avoidance of mu opioid-related CNS side effects, such as respiratory depression and euphoria;
- absence of euphoria which lowers addiction or abuse potential;
- avoidance of interactions with other drugs because, as a peptide composed of four non-natural D-amino acids that is not metabolized in the liver, CR845/difelikefalin does not interact with the liver enzymes responsible for the metabolism of most commonly used classes of drugs; and

- availability in injectable form for acute pain treatment as well as for treatment of pruritus in CKD patients undergoing hemodialysis in the hospital 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 (CKD-HD)	• Phase 3 U.S. efficacy trial ongoing; Phase 3 long term safety trial ongoing • Phase 2/3 adaptive trial completed (data released); end of Phase 2 meeting with FDA completed • Breakthrough Therapy Designation granted by FDA in June 2017	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus Chronic Kidney Disease-Hemodialysis (CKD-HD)	• Phase 1 safety and PK study completed	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus CKD (Stage III - V) (non-hemodialysis)	• Phase 1 safety and PK study in patients with Stage III-V CKD ongoing	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus Chronic Liver Disease (CLD)	• IND filed in 4Q 2017 • Phase 1 safety and PK trial initiated in 1Q 2018	Cara (Worldwide, other than South Korea); CKDP (South Korea)
Pain	CR845/difelikefalin Injection	Acute Post Operative Pain	• Phase 3 Adaptive trial ongoing; Interim conditional power analysis completed. Data expected in 2Q 2018	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 South Korea); 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 chronic kidney disease, or CKD, as well as with diseases such as atopic dermatitis, eczema, cholestatic liver disease and psoriasis. Based on KORSUVA (CR845/difelikefalin)'s effect on the peripheral nervous system and immune cells as well as KORSUVA (CR845/difelikefalin)'s anti-pruritic potency in preclinical models, we believe KORSUVA (CR845/difelikefalin) has the potential to treat pruritus across multiple medical conditions.

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

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. We also expect to initiate an international Phase 3 efficacy trial of KORSUVA (CR845/difelikefalin) injection in 2018. In addition to the efficacy trials, we are also conducting a 52-week Phase 3 safety study of KORSUVA (CR845/difelikefalin) injection in patients undergoing hemodialysis 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 top-line results from the Phase 2 clinical trial of KORSUVA (CR845/difelikefalin) injection in 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 Phase 3 Efficacy Trial of KORSUVA (CR845/Difelikefalin) Injection

In January, 2018 we initiated the first Phase 3 efficacy trial 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 ug/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 analysis that allows 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 validated 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.

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 who completed one of our prior Phase 2/3 trials of KORSUVA (CR845/difelikefalin) injection (CR845-CLIN2101 Part A or CR845-CLIN2005 Part B) 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 0.5ug/kg.

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 (0.5ug/kg, 1.0 ug/kg and 1.5 ug/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 standard NRS for itch. 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 endpoint of this trial focused on quality of life measures associated with pruritus using the Skindex-10 score, a validated self-assessment scale with higher scores indicating worse quality of life. Patients receiving I.V. CR845 experienced a 100% greater reduction from baseline in the average total Skindex-10 score at week eight versus those

receiving placebo (p<0.0007). The total average Skindex-10 score reflected statistically significant reductions in each of the three Skindex-10 domains: disease (p<=0.0001), mood/emotional distress (p=0.01) and social functioning (p=0.009). In a post-hoc analysis, (1) 64% of the patients treated at the 0.5 ug/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 ug/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 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 adverse events were transient paresthesia (i.e., primarily mid-facial tingling or numbness), somnolence and dizziness, as reported in previous clinical studies of KORSUVA (CR845/difelikefalin). Full results of this trial were presented at Kidney Week 2017, the American Society of Nephrology's Annual Meeting on November 2-4, 2017.

Phase 2 Efficacy Trial in Dialysis Patients (Part B)

Part B of the CLIN2005 study was a randomized, double-blind, placebo-controlled Phase 2 proof-of-concept trial, which measured the efficacy of KORSUVA (CR845/difelikefalin) injection compared to placebo in reducing the intensity of itch in dialysis patients with uremic pruritus over a two-week dosing period, who had baseline "worst itching" scores of greater than 40% on a visual analog scale, or VAS. The primary endpoint of the study was the change from baseline in the average "worst itching" scores during the second week of treatment, as recorded on a VAS. Secondary endpoints focused on quality of life measures associated with pruritus burden using a series of validated self-assessment scales. The study enrolled a total of 65 dialysis patients in the United States. 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, 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.

Phase 1b Safety and Pharmacokinetic Trial in Dialysis Patients (Part A)

In 2014, we conducted a Phase 1b clinical trial, which was part A of CLIN2005, a Phase 2 proof-of-concept trial of KORSUVA (CR845/difelikefalin) injection for the treatment of uremic pruritus. Part A was a double-blind, randomized, placebo-controlled trial designed to evaluate the safety and PK of KORSUVA (CR845/difelikefalin) injection in 24 hemodialysis patients. KORSUVA (CR845/difelikefalin) was administered in the form of intravenous bolus injection at doses ranging from 0.5 ug/kg to 2.5 ug/kg after each dialysis session up to three times per week. Pharmacokinetic analysis indicated that KORSUVA (CR845/difelikefalin) injection exhibited dose linear increases in maximum serum concentration and total KORSUVA (CR845/difelikefalin) exposure measured by AUC, with an approximate 10-fold increase in AUC across doses in these dialysis patients compared to normal subjects. KORSUVA (CR845/difelikefalin) injection was observed to be safe and well tolerated over the one-week dosing period. The most common AEs were transient facial tingling and headache. No serious AEs were reported. Although uremic pruritus was not an inclusion criterion for randomization, three subjects entered the trial with "worst itching" baseline scores in the moderate-to-severe range, > 4.0 on a 10.0-point VAS. All three of these subjects received dosing of KORSUVA (CR845/difelikefalin) injection up to three times per week (with two subjects receiving 1 ug/kg and one receiving 2.5 ug/kg) and ended the one-week dosing period with reported "worst itching" scores of 1.0 or less on a VAS.

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

In mid-2017, we announced top-line results from a Phase 1 safety and PK study of multiple doses of Oral KORSUVA (CR845/difelikefalin) in patients with CKD undergoing hemodialysis to define tablet strengths to inform our ability to develop an oral tablet formulation for the treatment of moderate-to-severe uremic pruritus. The Phase 1 results showed that all four tablet strengths of Oral KORSUVA (CR845/difelikefalin) (0.25, 0.5, 1.0 and 2.5 mg) were generally well-tolerated when administered either daily or after each dialysis session three times per week. Top-line PK analysis indicated that plasma levels of KORSUVA (CR845/difelikefalin) attained after oral administration of doses up to 2.5 mg were comparable to or exceeded those attained with clinically efficacious doses

of KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe CKD-aP in patients undergoing hemodialysis. The plasma levels of KORSUVA (CR845/difelikefalin) attained after oral administration of the 1.0 mg tablet strength approximated those attained with the 1.0 ug/kg KORSUVA (CR845/difelikefalin) injection dose, which demonstrated significant clinical benefit in our Phase 2/3 trial in patients undergoing hemodialysis with CKD-aP.

Overall, the frequency of treatment emergent adverse events, or TEAEs, in Oral KORSUVA (CR845/difelikefalin)-treated patients was similar to the group administered placebo. All TEAEs were generally mild and comparable to those reported in our Phase 2/3 trial after KORSUVA (CR845/difelikefalin) injection administration in CKD-aP patients undergoing hemodialysis. Absolute oral bioavailability of the 1.0 mg tablet strength was determined to be similar in CKD patients undergoing hemodialysis to that obtained in non-CKD patients.

In October 2017, we initiated a Phase 1 trial of Oral KORSUVA (CR845/difelikefalin) in patients with Stage III - V CKD (non-hemodialysis). The Phase 1 trial is designed to examine the PK and safety of up to four tablet strengths of Oral KORSUVA (CR845/difelikefalin) (0.25 mg, 0.5 mg, 1.0 mg and 2.5 mg), dosed daily over a one-week treatment period in up to 80 patients with stage III-V CKD (non-hemodialysis). Data from this trial will inform dose selection and design of a planned placebo-controlled Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) in patients with stage III-V CKD (non-hemodialysis) and hemodialysis patients with moderate-to-severe pruritus, which we plan to initiate in the first half of 2018.

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

CLD-aP manifests as “cholestasis” symptoms causing severe whole-body itch. It is an intense, intractable, debilitating condition that significantly disrupts patients’ daily activities and sleep, and consequently impairs their quality of life. Although the pathophysiology is not well understood, it is likely multi-factorial, involving immune system dysregulation (including elevated pro-inflammatory activity) and imbalance in the endogenous opioid system. Consequently, the use of selective kappa-opioid receptor agonists has been suggested for the treatment of pruritus in patients with 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 chronic liver disease in the first quarter of 2018. We aim to initiate a Phase 2 trial of Oral KORSUVA for the treatment of CLD-aP later this year.

Intravenous CR845/Difelikefalin for Treatment of Acute Postoperative Pain

We are also investigating 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 September 2015, we initiated our Phase 3 clinical trial program for CR845/difelikefalin injection in postoperative pain in an adaptive trial in patients undergoing a range of abdominal surgeries. This trial is 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 ug/kg, 2.0 ug/kg and 5.0 ug/kg), which were compared to placebo with an interim conditional power assessment to identify optimal doses to be used to complete the enrollment of this trial.

In June 2016, we modified the trial protocol and resumed the trial as a three-arm trial, testing two doses of I.V. CR845/difelikefalin (1.0 ug/kg and 0.5 ug/kg) versus placebo, based on a safety review by us, the trial’s Independent Data Monitoring Committee, or 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 revised trial is enrolling up to 450 patients within the United States undergoing abdominal surgeries, all of which are associated with moderate-to-severe postoperative pain. The primary efficacy endpoint is the Change in Pain Intensity over the 24-hour postoperative period using a common measurement method known as area under the curve, or AUC, using the patient-reported NRS score collected at pre-specified time points through 24 hours post-surgery. Postoperative nausea and vomiting is also being evaluated as a secondary efficacy endpoint.

In June 2017, we announced the completion of a prespecified interim conditional power analysis of our adaptive Phase 3 trial of CR845/difelikefalin injection. Based on the guidance of the IDMC, the trial is continuing in accordance with its current protocol, testing two doses of CR845/difelikefalin injection (1.0 ug/kg and 0.5 µg/kg I.V.) versus placebo in up to 450 patients undergoing abdominal surgery. The IDMC also reviewed the available safety information, including serum sodium levels, and confirmed that both doses of CR845/difelikefalin injection were observed to be well tolerated with no significant changes in the monitored safety parameters. We expect data from this trial in the second quarter of 2018.

Phase 1 and 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. According to research conducted at Duke University, post-operative AEs, such as nausea and vomiting associated with currently approved opioids, increase the length of time that a patient spends in the hospital and increases the cost of caring for those patients. Therefore, we believe that if successful, CR845/difelikefalin injection administered in a post-surgical setting has the potential to significantly reduce the length of hospital stays, thereby reducing overall healthcare costs.

The safety profile of CR845/difelikefalin injection has been demonstrated in six Phase 1 and three Phase 2 acute pain studies. In these trials, CR845/difelikefalin injection was administered to approximately 970 human subjects at single or repeat doses ranging from 1ug/kg to 40 ug/kg up to a 1-week period, in the form of intravenous infusion or bolus injection. CR845/difelikefalin injection was considered to be generally safe and 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 the characteristic CNS-related adverse events, such as acute psychiatric side effects, 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 CR845/difelikefalin injection met the trial's primary endpoint by demonstrating highly statistically significant lower "drug liking" scores as measured by VAS Emax ($p < 0.0001$) when compared to pentazocine, 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 opioid for acute pain or pruritus. Data from this trial were also presented at PAINWEEK in September 2015 in Las Vegas, Nevada.

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 ug/kg) and I.V. CR845/difelikefalin (5.0 ug/kg) on sequential 24-hour periods, with I.V. CR845/difelikefalin (5.0 ug/kg) representing a projected five-fold supra-therapeutic dose. After each administration, and continuing through four hours post-dosing, end-tidal CO_2, or $ETCO_2$, oxygen saturation, or SpO_2, and respiratory rate were continuously monitored. The primary safety endpoints were: a >10 mmHg sustained ($\geq$30 seconds duration) increase in $ETCO_2$ above baseline or to >50 mmHg, and a sustained reduction in SpO_2 to <92 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. Full data from this study were also presented at the American Society of Anesthesiologists' annual meeting in Boston in October, 2017.

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. We believe Oral CR845/difelikefalin can potentially address a significant unmet medical need for a safer alternative to opioids, NSAIDs or CNS anticonvulsant agents for the treatment of moderate-to-severe acute and chronic pain. In addition to the efficacy benefits that CR845/difelikefalin has previously demonstrated, we believe, if successful, a significant benefit of Oral CR845/difelikefalin in the acute and chronic pain market could be its lack of CNS side effects, including euphoria, which should preclude the misuse, abuse and addiction risks associated with currently approved mu opioids.

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); all patients (OA of the knee or hip) maintained on the 5.0 mg dose to the end of the eight-week treatment period exhibited a 35% reduction in mean joint pain score versus placebo, which did not reach statistical significance (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. Full results from this trial were presented at the American College of Rheumatology’s Annual Meeting held in November 2017.

Phase 2a Trial of Oral CR845/Difelikefalin

In August 2015, we advanced our tablet formulation of Oral CR845/difelikefalin into a Phase 2a clinical trial in patients with osteoarthritis, or OA, of the knee or hip. The Phase 2a trial was a single-blind, randomized, multiple ascending dose trial designed to evaluate the safety, PK and effectiveness of Oral CR845/difelikefalin tablets dosed over a two-week treatment period in OA patients experiencing moderate-to-severe pain. Patients discontinued current pain medications five days prior to baseline measurements. Four tablet strengths (0.25 mg, 0.5 mg, 1.0 mg and 5.0 mg) were administered twice a day over a two-week treatment period in a total of 80 OA patients. In addition to safety and PK observations, CR845/difelikefalin 's effectiveness was assessed by: change from baseline in joint pain using the NRS score, change from baseline in the Western Ontario and McMaster Osteoarthritis Index, or WOMAC, change from baseline in rescue medication use, and Patient Global Assessment, or PGA. Acetaminophen was the only allowable rescue medication. PK analyses indicated dose-proportional exposure of CR845/difelikefalin after oral administration, with the 5.0 mg dose group exhibiting an approximately five-fold increased mean AUC value compared to the 1.0 mg dose group.

In December 2015, we announced positive top-line results from this Phase 2a trial. The results showed a dose-related reduction in mean joint pain score after two weeks of treatment (from baseline) ranging from 25% reduction at the lowest dose (0.25 mg) to up to 34% reduction for the highest (5.0 mg) dose. Additionally, a post-hoc analysis also showed that the reduction in pain score in the 5.0 mg dose group was accompanied by a statistically significant reduction in mean rescue medication of approximately 80% (p= 0.02, for 5.0 mg vs lower dose groups). The effectiveness of the 5.0 mg dose was further supported by statistically significant, dose-related increases in the proportion of patients whose OA was "very much improved" or "much improved" as indicated by patient global assessment (p=0.02). In this trial, all four tablet strengths were observed to be safe and well tolerated.

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. We are developing lead molecules that selectively modulate peripheral CB receptors without targeting CNS cannabinoid receptors.

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.

We have completed pre-GLP safety studies with CR701 and are exploring the option of conducting the necessary GLP studies (safety studies conducted under the regulatory standard of Good Laboratory Practices) necessary to file an IND with the FDA to initiate a Phase 1 ascending single-dose tolerance and PK study in healthy human subjects.

Commercial Partnerships

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 related to CR845/difelikefalin. We are also eligible to receive a one-time sales milestone of one billion Yen (approximately $9.4 million based on the U.S. Dollar/Yen exchange rate as of March 8, 2018) 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. Ten 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, 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 thirteen 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 and 9,359,399) 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, 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. Patent applications claiming CR845/difelikefalin are pending in Brazil and India.

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, Hong Kong, Israel, Japan, Malaysia, Mexico, New Zealand, Philippines, Singapore, Russia and South Africa. These and any other patents resulting from the pending national patent applications, if issued, expire no earlier than June 20, 2028. Patent applications claiming CR701 are pending in Brazil, China, India and South Korea.

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 have been maintained in Brazil, Canada, China, France, Germany, India, Italy, Russia, Spain and the U.K. and are due to expire 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, naltrexone, and UVB light therapy, generally with limited success.

Because of the substantial unmet need for products that are safe and effective in CKD-aP, there are other companies involved in the discovery, development, and/or marketing of such products. Such product candidates include nalbuphine from Trevi Therapeutics, asimadoline from Tioga Pharmaceuticals, 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.

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 Vicodin® (hydrocodone and acetaminophen) and 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 and one secondary 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;

- 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.

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 user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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 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. Additionally, 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, such as 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 criminal and significant civil monetary 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, at the federal level, there have been several recent U.S. Congressional inquiries and proposed bills 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. 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 agree to offer 50% 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 designed to delay the implementation of any 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". Additionally, 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.

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, will remain in effect until 2025, 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 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.

Research and Development

Conducting R&D is central to our business model. We have invested and expect to continue to invest significant time and capital in our R&D operations. Our R&D expenses were $48.5 million, $49.3 million and $21.2 million in 2017, 2016 and 2015, respectively. We anticipate that our R&D expenses will increase for the foreseeable future as we seek to develop I.V. CR845/difelikefalin and Oral CR845/difelikefalin in multiple indications.

Employees

As of March 15, 2018, we had 37 employees, all of whom are located in the United States. None of our employees is 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.

In addition, the public may read and copy any materials that we file with or furnish to the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. 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 $58.1 million. $57.3 million and $24.7 million for the years ended December 31, 2017, December 31, 2016 and December 31, 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $220.3 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 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 other diseases associated with pruritus;
- continue our I.V. CR845/difelikefalin clinical trial program in acute pain;
- 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.

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.

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 our lead product candidates, 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, including I.V. and Oral CR845/difelikefalin, is expensive. We will need to raise additional capital to:

- fund our future clinical trials;
- fund our operations and continue our efforts to hire additional personnel and build a commercial infrastructure to prepare for the commercialization of I.V. CR845/difelikefalin and our other future product candidates, if approved by the FDA;
- qualify and outsource the commercial-scale manufacturing of our products under cGMP;
- progress our KORSUVA (CR845/difelikefalin) injection CKD-aP program through Phase 3 pivotal trials;
- expand the use of Oral KORSUVA (CR845/difelikefalin) in other pruritic indications;
- advance I.V. CR845/difelikefalin for acute pain through NDA submission; and
- in-license other product candidates.

We believe that with our available cash and cash equivalents and marketable securities balances as of December 31, 2017, we will have sufficient funds to meet our projected operating requirements into the first half of 2019, 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 the completion of our development of KORSUVA (CR845/difelikefalin) injection and Oral KORSUVA (CR845/difelikefalin) in uremic pruritus as well as in other pruritic indications such as 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 potential for delays in our efforts to seek regulatory approval for I.V. CR845/difelikefalin for acute pain, and any costs associated with such delays;
- the costs of establishing a commercial organization to sell, market and distribute I.V. CR845/difelikefalin, if approved;
- the rate of progress and costs related to our Phase 2 development of Oral KORSUVA (CR845/difelikefalin) and our Phase 3 development of KORSUVA (CR845/difelikefalin) injection for uremic pruritus;
- the rate of progress and costs of our efforts to prepare for the submission of an NDA for I.V. CR845/difelikefalin, Oral CR845/difelikefalin 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 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin, 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, I.V. CR845/difelikefalin, 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 our most advanced product candidate, I.V. CR845/difelikefalin. Our business depends entirely on the successful development and commercialization of our product candidates, and in particular, I.V. CR845/difelikefalin, 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 I.V. CR845/difelikefalin. We currently generate no revenues from sales of any products, and we may never be able to develop or commercialize a marketable product.

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 CKD-aP. In March 2017, we announced top-line data from the Phase 2 trial. In September 2017, we held an End-of-Phase 2 Meeting with the FDA. We, in consultation with the FDA, have established the key elements of the Phase 3 program to support an NDA for KORSUVA (CR845/difelikefalin) injection for the treatment of moderate-to-severe CKD-aP in patients undergoing hemodialysis. In January 2018, we initiated the first pivotal randomized, double-blind, placebo-controlled Phase 3 trial in patients undergoing hemodialysis with moderate-to-severe CKD-aP. We initiated the first clinical trial for I.V. CR845/difelikefalin in acute pain in the third quarter of 2015. As described elsewhere in this report, in February 2016, the FDA placed the trial on clinical hold pending a safety review following the triggering of a stopping rule in the trial protocol. The clinical hold was removed in April 2016 and we resumed the clinical trial in June 2016. In June 2017, we announced the completion of a prespecified interim conditional power analysis of this trial. Based on the results of this analysis, the trial will continue in accordance with its current protocol. We expect completion of enrollment within the first half of 2018. We cannot give you any assurance that these trials will be completed within a specified period of time or at all, and if they are completed, we cannot assure you that they will successfully support our regulatory applications for approval.

In addition to this clinical development, 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 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, CR845/difelikefalin injection we will not be able to generate revenue from CR845/difelikefalin injection 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 I.V. CR845/difelikefalin or any of our other product candidates will be successful in clinical trials or receive regulatory approval. Even though I.V. CR845/difelikefalin has completed three Phase 2 clinical trials and has begun its Phase 3 clinical trial program for

the treatment of acute postoperative pain, 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, including our Phase 3 clinical trial(s) for the treatment of CKD-aP. Further, our product candidates, including I.V. CR845/difelikefalin, 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 CR845/difelikefalin injection will depend on our ability to:

- create market demand for I.V. CR845/difelikefalin through our own marketing and sales activities, and any other arrangements to promote this product candidate we may otherwise establish;
- hire, train and deploy a sales force to commercialize I.V. CR845/difelikefalin in the United States;
- manufacture I.V. CR845/difelikefalin 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;
- create partnerships with, or offer licenses to, third parties to promote and sell I.V. CR845/difelikefalin in foreign markets where we receive marketing approval;
- maintain patent and trade secret protection and regulatory exclusivity for I.V. CR845/difelikefalin;
- launch commercial sales of I.V. CR845/difelikefalin, whether alone or in collaboration with others;
- achieve market acceptance of I.V. CR845/difelikefalin by patients, the medical community and third-party payers;
- achieve coverage and adequate reimbursement for I.V. CR845/difelikefalin;
- effectively compete with other therapies; and
- maintain a continued acceptable safety profile of I.V. CR845/difelikefalin following launch.

As we continue to develop our other product candidates, including Oral 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 I.V. CR845/difelikefalin.

Our lead product candidate, I.V. CR845/difelikefalin, and our second product candidate, Oral CR845/difelikefalin, act as selective kappa opioid receptor agonists, which is a drug class that has not previously yielded a successful commercial product for 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 I.V. CR845/difelikefalin for CKD-aP and acute postoperative pain and Oral CR845/difelikefalin for CKD-aP. 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 I.V. CR845/difelikefalin and Oral 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 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, 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 ongoing 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 I.V. CR845/difelikefalin belongs to, have been associated with poorly tolerated psychiatric side effects, such as a feeling of emotional and mental discomfort, or dysphoria, and hallucinations, at high doses, particularly for prior generations of kappa opioid agonists with substantially unrestricted or only partially restricted entry to the CNS. Although we have not observed psychiatric side effects in any CR845/difelikefalin clinical trials to date, we cannot be certain that these side effects or others will not be observed in the future, or that the FDA will not require additional trials or impose more severe labeling restrictions due to these side effects or other concerns. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients, if not already required pursuant to a REMS;

- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

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

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue conducting clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the eligibility criteria for, and design of, the trial in question;
- the perceived risks and benefits of the product candidate under study;
- competition in recruiting and enrolling patients in clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Our current development plan for I.V. CR845/difelikefalin contemplates recruiting and enrolling more than a thousand patients for our Phase 3 clinical trials. 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.

Our lead product candidate, I.V. CR845/difelikefalin, and our second product candidate, Oral CR845/difelikefalin, if approved, will compete 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. We cannot predict whether REMS will be required as part of the FDA's approval of our product candidates and, if required, what those requirements might be. Any limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of our product candidates, if approved. If a REMS program is required, depending on the extent of the REMS requirements, the program might significantly increase our costs to commercialize these product candidates. Furthermore, risks of our product candidates that are not adequately addressed through proposed REMS for such product candidates may also prevent or delay their approval for commercialization.

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

The results from our HAL trial suggest that CR845/difelikefalin may have the potential to be a Schedule V or non-scheduled peripheral opioid. However, while CR845/difelikefalin -based products have not demonstrated any evidence of the euphoria that has led to misuse, abuse, and addiction of mu opioids, and while CR845/difelikefalin-based products are not being treated as a controlled substance in clinical trials, it is possible that the DEA could determine that CR845/difelikefalin-based products should be regulated as controlled substances.

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

If any of our product candidates are classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors would be required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. Also, if any of our product candidates were classified as controlled substances, there is a risk that DEA regulations could limit the supply of the compounds used in clinical trials and, in the future, the ability to produce and distribute our products in the volume needed to meet commercial demand.

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

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

We have received conditional approval from the FDA for the use of KORSUVA as the proprietary name for our product candidate I.V. CR845/difelikefalin for the treatment of itch. 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 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 and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or 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 ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

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

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

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

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

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and cGCPs for any clinical trials that we conduct post-approval. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including any requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

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

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

- restrictions on manufacturing such products;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;

- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

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

Risks Related to the Commercialization of Our Product Candidates

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

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

Specifically, 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. Similarly, 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, Trevi, Tioga, Leo Pharma, Chugai and others.

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 I.V. CR845/difelikefalin is approved by the FDA, we plan to build a commercial infrastructure, including our own specialty sales force, to launch CR845/difelikefalin injection in the hemodialysis and the acute care 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, we intend to commercialize I.V. CR845/difelikefalin and Oral CR845/difelikefalin outside the United States with a marketing and sales collaborator or collaborators, rather than with our own 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 future 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 I.V. CR845/difelikefalin or any of our other product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our efforts to commercialize I.V. CR845/difelikefalin or our other product candidates on our own include:

- our inability to recruit, train, manage and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe I.V. CR845/difelikefalin or our other product candidates;
- our 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin. 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 I.V. CR845/difelikefalin 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.

If I.V. or Oral CR845/difelikefalin 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 I.V. CR845/difelikefalin, Oral 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, 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 I.V. CR845/difelikefalin, Oral CR845/difelikefalin and any of our other product candidates by physicians, hospitals, 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 adequate coverage or reimbursement by third parties, 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 is approved.

Our ability to effectively promote and sell I.V. CR845/difelikefalin, Oral 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 hospital or dialysis organization formularies, and our ability to obtain sufficient third-party coverage or reimbursement. Generally, before we can attempt to sell I.V. CR845/difelikefalin in a hospital or dialysis provider, I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin. 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 I.V. CR845/difelikefalin, Oral 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 I.V. CR845/difelikefalin, 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 I.V. CR845/difelikefalin or other product candidates that we may develop and may have to limit their commercialization.

The use of I.V 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. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage to include the sale of commercial products if we obtain FDA approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that

had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

Risks Related to Our Dependence on Third Parties

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

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

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

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

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be

no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

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

We do not manufacture any of our product candidates, and we do not currently plan to develop any capacity to do so. We 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 I.V. CR845/difelikefalin, 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 I.V. CR845/difelikefalin 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 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 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 I.V. CR845/difelikefalin 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 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. Both 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 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 have entered into license agreements with Maruishi and CKDP to develop, manufacture and commercialize products containing CR845/difelikefalin (both I.V. and Oral) in Japan and South Korea, respectively. In addition to our existing agreements covering Japan and Korea, 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, both the Maruishi and CKDP Agreements may be terminated by our collaborator for our breach or insolvency, 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin and to make it readily available at the point of care throughout their hospitals.

In addition to extensive internal efforts, the successful commercialization of I.V. CR845/difelikefalin will require many third parties, over whom we have no control, to decide to utilize I.V. CR845/difelikefalin and to make it readily available at the point of care throughout their hospitals. These third parties include physicians, pharmacists, and hospital pharmacy and therapeutics committees, which are commonly referred to as P&T committees. Generally, even if I.V. CR845/difelikefalin is approved by the FDA, before we can attempt to sell I.V. CR845/difelikefalin in a hospital, I.V. CR845/difelikefalin must be approved for addition to that hospital's list of approved drugs, or formulary list, by the hospital's P&T committee. A hospital's 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 hospitals 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, hospital pharmacists may be concerned that the cost of acquiring I.V. CR845/difelikefalin for use in their institutions will adversely impact their overall pharmacy budgets, which could cause pharmacists to resist efforts to add I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin 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 hospital pharmacists quickly enough to maintain and grow hospital sales of I.V. CR845/difelikefalin.

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 privacy and security 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;
- HIPAA, as amended by HITECH, and their implementing regulations, and as amended again by the Final HIPAA Omnibus Rule, Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification Rules Under HITECH and the Genetic Information Nondiscrimination Act; Other Modifications to HIPAA, published in January 2013, which 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;
- 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 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 payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing 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.

Because of the breadth of these laws and the narrowness of the statutory exceptions and 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 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 privacy, security, 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.

If the government or other third-party payers fail to provide coverage and adequate reimbursement and payment rates for I.V. CR845/difelikefalin 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. In particular, 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. Also, I.V. CR845/difelikefalin 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. 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, I.V. CR845/difelikefalin 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. Adequate third-party coverage and 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 agree to offer 50% 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, that began in 2011;
- 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 False Claims Act and the 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 designed to delay the implementation of any 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 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". Additionally, 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. We cannot predict how the Health Care Reform Law, its possible repeal, or any legislation that may be proposed to replace the Health Care Reform Law will impact 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, will remain in effect until 2025, 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, at the federal level, there have been several recent U.S. Congressional inquiries and proposed bills 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. 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 recently enacted Drug Supply Chain Security Act, imposes new obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing, which will be phased in over several years beginning in 2015. Among the requirements of this new legislation, manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product. The transfer of information to subsequent product owners by manufacturers will eventually be required to be done electronically. Manufacturers will also be required to verify that purchasers of the manufacturers' products are appropriately licensed. Further, under this new legislation, manufacturers will have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

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 European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. 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 maintained in confidence for at least 18 months after their earliest effective filing date. 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. In the event that a third party has also filed a U.S. patent application relating to our product candidates or a similar invention, 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. 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 may 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, 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin or our other product candidates may infringe. There could also be existing patents of which we are not aware that I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin, Oral 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 I.V. CR845/difelikefalin; (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

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

As of March 15, 2018, we had 37 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 I.V. CR845/difelikefalin, 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 I.V. CR845/difelikefalin, 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, 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.

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

Despite our implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed.

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 8, 2018, 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 Phase 3 clinical trials for I.V. CR845/difelikefalin;
- any delay or refusal on the part of the FDA in approving an NDA for I.V. CR845/difelikefalin or our other product candidates;
- the commercial success of I.V. CR845/difelikefalin, Oral CR845/difelikefalin or our other product candidates, if approved by the FDA;
- results of clinical trials of I.V. CR845/difelikefalin, Oral 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;
- 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 I.V. CR845/difelikefalin, Oral 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 I.V. CR845/difelikefalin or our other product candidates, which would likely further delay any such approval;
- if I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin 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 I.V. CR845/difelikefalin, our other product candidates, or the product candidates of our competitors; and
- if I.V. CR845/difelikefalin or other product candidates receives regulatory approval, the level of underlying hospital 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 as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an emerging growth company 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 the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering, which is December 31, 2019, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. To the extent that we are no longer eligible to use exemptions from various reporting requirements under the JOBS Act, 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 carryforwards and R&D tax credits may expire and not be used. As of December 31, 2017, we had federal and state net operating loss carryforwards of approximately $205.1 million and $198.4 million, respectively, and we also had federal and state R&D tax credit carryforwards of approximately $7.4 million and $1.0 million, respectively. Our net operating loss 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 tax credits will begin expiring in 2025 unless previously used. Under the Tax Cuts and Jobs Act of 2017, the use of NOL's generated after December 31, 2017 will be subject to a limitation of 80% of taxable income and can be carried forward indefinitely but carryback is generally prohibited. To the extent that we have not exchanged our Connecticut research tax credits for a tax refund, those tax credits carryforward indefinitely. Additionally, our ability to use any net operating loss and 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 and 2017, together with private placements and other transactions that have occurred, may trigger, or may have already triggered such an ownership change. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further 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 net operating loss carryforwards and research 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 net operating loss carryforwards and research tax credits before they expire. In addition, certain states have suspended use of net operating loss 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 net operating loss 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 adjusted earnings, eliminates net operating loss 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 16 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 are subject to litigation and claims arising in the ordinary course of business. We are not currently a party to any material legal proceedings and we are not aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results or financial condition.

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". The following table sets forth the high and low daily sale prices for our common stock for each calendar quarter during 2016 and 2017, as reported on the Nasdaq Global Market:

Fiscal 2017	High	Low
First Quarter (January 1, 2017 to March 31, 2017)	$ 20.90	$ 9.35
Second Quarter (April 1, 2017 to June 30, 2017)	$ 28.50	$ 14.15
Third Quarter (July 1, 2017 to September 30, 2017)	$ 17.48	$ 11.83
Fourth Quarter (October 1, 2017 to December 31, 2017)	$ 14.25	$ 11.11

Fiscal 2016	High	Low
First Quarter (January 1, 2016 to March 31, 2016)	$ 17.69	$ 4.26
Second Quarter (April 1, 2016 to June 30, 2016)	$ 9.00	$ 4.35
Third Quarter (July 1, 2016 to September 30, 2016)	$ 8.90	$ 4.75
Fourth Quarter (October 1, 2016 to December 31, 2016)	$ 12.74	$ 5.85

The last reported sale price of our common stock as reported on The Nasdaq Global Market on March 8, 2018 was $14.32 per share.

Stockholders

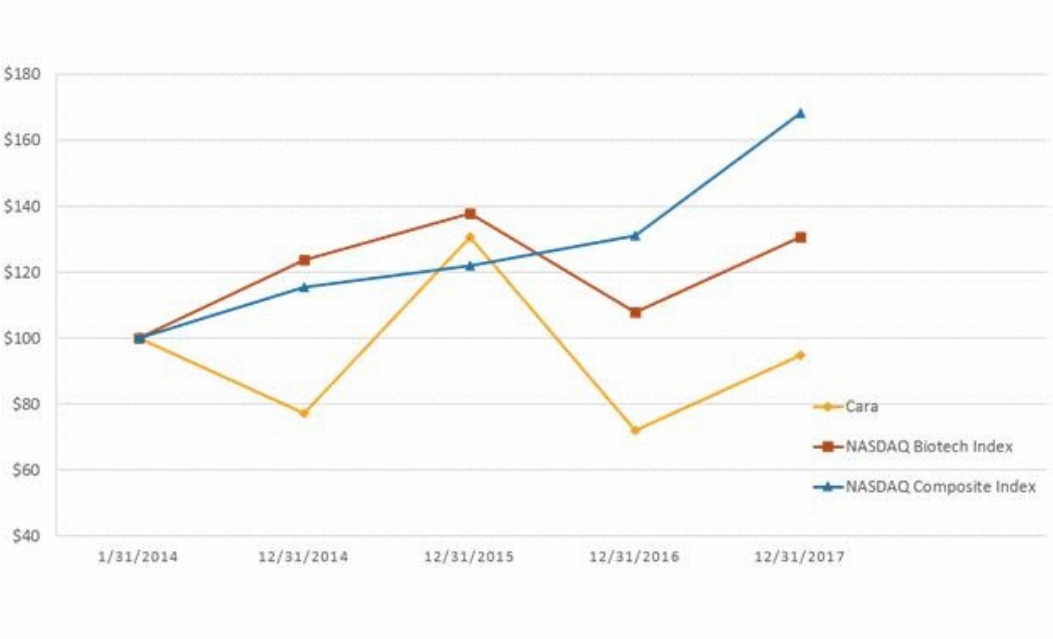
As of March 8, 2018, there were 39 holders of record of our common stock. This number does not reflect the beneficial holders of our common stock who hold shares in street name through brokerage accounts or other nominees.

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.

The Company's Stock Performance

The following graph compares cumulative total return of the Company's 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 the Company's stock was traded on the Nasdaq Global Market) in each of the Company's 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
Cara Therapeutics, Inc.	100	77.23	130.60	71.96	94.81
NASDAQ Biotechnology	100	123.71	137.83	107.94	130.67
NASDAQ Composite	100	115.40	122.02	131.17	168.22

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, 2017, 2016 and 2015 and as of December 31, 2017 and 2016 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, 2014 and 2013 and as of December 31, 2015, 2014 and 2013 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,				
	2017	2016	2015	2014	2013
	(in thousands, except share and per share data)				
Statement of Operations Data:					
Revenue:					
License and milestone fee revenue	$ 530	$ —	$ 1,710	$ 302	$ 9,637
Collaborative revenue	313	—	2,093	2,201	2,225
Clinical compound revenue	68	86	—	674	102
Total revenue (1)	911	86	3,803	3,177	11,964
Operating expenses:					
Research and development	48,524	49,253	21,221	15,068	8,685
General and administrative	11,872	9,233	7,770	6,181	3,516
Total operating expenses	60,396	58,486	28,991	21,249	12,201
Operating loss	(59,485)	(58,400)	(25,188)	(18,072)	(237)
Other income (expense), net (2)	1,156	652	101	126	(3,756)
Loss before benefit from income taxes	(58,329)	(57,748)	(25,087)	(17,946)	(3,993)
Benefit from income taxes	204	468	397	201	30
Net loss	$ (58,125)	$ (57,280)	$ (24,690)	$ (17,745)	$ (3,963)
Net loss available to common stockholders	$ (58,125)	$ (57,280)	$ (24,690)	$ (17,745)	$ (3,072)
Net loss per share available to common stockholders:					
Basic and Diluted	$ (1.86)	$ (2.10)	$ (1.00)	$ (0.85)	$ (0.74)
Weighted average shares:					
Basic and Diluted	31,202,842	27,279,008	24,620,372	20,965,935	4,133,138

	As of December 31,				
	2017	2016	2015	2014	2013
	(in thousands)				
Balance Sheet Data:					
Cash and cash equivalents and marketable securities (3)	$ 92,569	$ 58,276	$ 106,740	$ 52,663	$ 12,357
Total assets	97,004	63,828	110,897	55,934	18,083
Deferred revenue	—	—	—	1,452	3,475
Total liabilities	10,224	13,103	5,853	4,272	6,572
Total convertible preferred stock (4)	—	—	—	—	65,586
Total stockholders' equity (deficit)	86,780	50,725	105,044	51,662	(54,075)

(1) The changes in revenue for the years ended December 31, 2013 through December 31, 2015 and December 31, 2017 reflect upfront payments in connection with our entering into a license agreement with Maruishi in 2013, continuing 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 and a sub-license fee payment received from Maruishi in 2017 (refer to the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations — Collaborations with Maruishi and CKDP, Results of Operations" and Note 11 of Notes to Financial Statements, *Collaborations*, in this Annual Report on Form 10-K).

(2) The decrease in interest expense from the year ended December 31, 2013 to the year ended December 31, 2014 was due to the conversion of the outstanding convertible promissory notes during 2013.

(3) The increases in cash and cash equivalents and marketable securities from December 31, 2016 to December 31, 2017, December 31, 2014 to December 31, 2015 and from December 31, 2013 to December 31, 2014 reflects the proceeds from our follow-on offering of our common stock, which closed on April 5, 2017, our follow-on offering of our common stock, which closed on August 4, 2015, and the proceeds from our IPO, which closed on February 5, 2014, respectively (refer to Note 9 of Notes to Financial Statements, *Stockholders' Equity,* in this Annual Report on Form 10-K).

(4) The decrease in convertible preferred stock from December 31, 2013 to December 31, 2014 was a result of the automatic conversion of all outstanding shares of our convertible preferred stock to common stock upon the closing of our IPO on February 5, 2014.

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

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

Overview

Introduction

We are a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus and pain by selectively targeting kappa opioid receptors. We are developing a novel and proprietary class of product candidates, led by KORSUVA™ (CR845/difelikefalin), that target the body's peripheral nervous system and certain immune cells. The FDA has conditionally accepted KORSUVA as the trade name for CR845/difelikefalin, an investigational drug product for the treatment of itch, whose safety and efficacy have not been fully evaluated by any regulatory authority. In Phase 2 trials, KORSUVA (CR845/difelikefalin) has demonstrated statistically significant reductions in itch intensity and concomitant improvement in quality of life measures in hemodialysis patients with moderate-to-severe chronic kidney disease-associated pruritus (CKD-aP) and is currently being investigated in Phase 3 trials in hemodialysis patients with CKD-aP. In addition, CR845/difelikefalin has also demonstrated initial signs of efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics. See Part I, Item 1, Business in this Annual Report on Form 10-K for a more detailed discussion of our product candidate pipeline and clinical development.

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-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.

Collaborations with Maruishi and CKDP

To date, we have entered into two license agreements relating to the development of CR845/difelikefalin.

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 another Japanese pharmaceutical company 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 near future. Substantially all of our revenue recognized to date has consisted of upfront, 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. To date, we have earned a total of $5.2 million in clinical development or regulatory milestone payments and sub-license fees, net of contractual foreign currency adjustments and South Korean withholding taxes, but have not received any royalties, under these 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, facilities expenses, including overhead expenses, 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 and other outside expenses. Our R&D expenses also included expenses related to preclinical activities, such as drug discovery, target validation and lead optimization for CR845/difelikefalin and our other, 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 2018 will increase over those for 2017. However, it is difficult to determine with certainty the duration and completion costs of our current or future preclinical 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:

- 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 significant costs include facility costs not otherwise included in R&D expenses, legal fees, insurance costs, investor relations costs, patent costs and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will continue near their current level through 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 and accountants, and investor relations costs. 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, 2017, 2016 and 2015

Revenue

	Year Ended December 31,				
	2017	2016			2015
	Dollar amounts in thousands				
		% change		% change	
License and milestone fee revenue	$ 530	-100%	$ —	-100%	$ 1,710
Collaborative revenue	313	-100%	—	-100%	2,093
Clinical compound revenue	68	-21%	86	100%	—
Total revenue	$ 911	959%	$ 86	-98%	$ 3,803

License and milestone fee revenue

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 Pharmaceuticals, Co. Ltd. that was allocated to the license fee deliverable under the Maruishi Agreement (see Note 11 of Notes to Financial Statements, *Collaborations*, in this Annual Report on Form 10-K).

License and milestone fee revenue for the year ended December 31, 2015, consisted of $1.1 million of the $1.7 million milestone payment earned in September 2015 under the Maruishi Agreement, which was attributable to the previously delivered license, and $0.6 million from the two milestone payments earned by us under the CKDP Agreement in July and September 2015.

Collaborative revenue

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 Pharmaceuticals, Co. Ltd. that was allocated to the R&D services deliverable under the Maruishi Agreement.

Collaborative revenue for the year ended December 31, 2015 consists of $0.6 million of the $1.7 million milestone payment earned in September 2015 under the Maruishi Agreement, which was attributable to the fully-delivered R&D services deliverable, and $1.5 million of revenue that had been deferred upon entry into the Maruishi Agreement.

Clinical compound revenue

Clinical compound revenue for the years ended December 31, 2017 and 2016 relate to the sale of clinical compound to Maruishi.

Research and Development Expense

	Year Ended December 31,				
	2017		2016		2015
	Dollar amounts in thousands				
		% change		% change	
Direct clinical trial costs	$ 34,075	-9%	$ 37,257	175%	$ 13,560
Consultant services in support of clinical trials	1,959	5%	1,860	86%	999
Stock-based compensation	2,433	87%	1,301	21%	1,073
Depreciation and amortization	418	-50%	839	88%	447
Other R&D operating expenses	9,639	21%	7,996	56%	5,142
Total R&D expense	$ 48,524	-1%	$ 49,253	132%	$ 21,221

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 16 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.

For the year ended December 31, 2016 compared to the year ended December 31, 2015, the net increase in direct clinical trial costs and related consultant costs primarily resulted from increases totaling $22.3 million related to the Phase 2/3 I.V. KORSUVA (CR845/difelikefalin) clinical trial in patients with uremic pruritus, the Phase 2b clinical trial of Oral CR845/difelikefalin in OA patients, the Phase 3 I.V. CR845/difelikefalin adaptive clinical trial and the Phase 1 trial of Oral KORSUVA (CR845/difelikefalin) in hemodialysis patients, coupled with a net increase of $2.7 million of CR845/difelikefalin drug manufacturing costs and a net increase of $4.0 million for toxicology studies. Those costs were partially offset by decreases totaling $4.4 million in clinical trial costs primarily in connection with the completion of the Phase 2a Oral CR845/difelikefalin clinical trial in patients with OA, in the fourth quarter of 2015, and the completion of the Phase 2a I.V. KORSUVA (CR845/difelikefalin) proof-of-concept trial in patients with uremic pruritus, in the third quarter of 2015. The increase in stock-based compensation expense relates primarily to increased employee headcount, partially offset by a decrease in expense related to stock option awards granted to non-employee consultants, which are marked to market each quarter, due to the decrease in the market price of our common stock. The increase in depreciation and amortization expense 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 (see Note 16 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 payroll and related costs associated with R&D personnel and rent, which includes recognition of all of the remaining rent expense allocable to research and development activities due during the remaining term of the Shelton operating lease (see Note 16 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K).

The following table summarizes our R&D expenses by product candidate for the years ended December 31, 2017, 2016 and 2015:

	Year Ended December 31,				
	2017		2016		2015
	Dollar amounts in thousands				
		% change		% change	
External research and development expenses:					
I.V. CR845 - Pain	$ 13,226	8%	$ 12,202	152%	$ 4,835
I.V. CR845 - Pruritus	7,566	-31%	11,042	206%	3,613
Oral CR845 - Pain	8,648	-19%	10,734	76%	6,103
Oral CR845 - Pruritus	6,594	28%	5,139	100%	—
Internal research and development expenses	12,490	23%	10,136	52%	6,670
Total research and development expenses	$ 48,524	-1%	$ 49,253	132%	$ 21,221

General and Administrative Expense

	Year Ended December 31,				
	2017		2016		2015
	Dollar amounts in thousands				
		% change		% change	
Professional fees and public/investor relations	$ 2,252	11%	$ 2,032	8%	$ 1,883
Stock-based compensation	3,897	160%	1,499	4%	1,441
Depreciation and amortization	77	-88%	626	60%	392
Other G&A operating expenses	5,646	11%	5,076	25%	4,054
Total G&A expense	$ 11,872	29%	$ 9,233	19%	$ 7,770

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.

For the year ended December 31, 2016 compared to the year ended December 31, 2015, the increase in professional fees and public/investor relations costs primarily included increases in public/investor relations costs and in accounting and auditing fees. The increase 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 (see Note 16 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K). The increase in other G&A operating expenses included increases in payroll and related costs and in insurance and rent, which includes recognition of all of the remaining rent expense allocable to general and administrative activities due during the remaining term of the Shelton operating lease (see Note 16 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K).

Other Income

	Year Ended December 31,				
	2017	2016		2015	
	Dollar amounts in thousands				
		% change		% change	
Other income	$ 1,156	77%	$ 652	547%	$ 101

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.

For the year ended December 31, 2016 compared to the year ended December 31, 2015, the increase in other income was primarily due to (1) an increase in interest income and dividends earned on our portfolio of investments, which included marketable securities during the entire year ended December 31, 2016 but only during the last month of the year ended December 31, 2015; (2) higher interest rates in the 2016 period and a higher average balance of cash and cash equivalents and marketable securities in the year ended December 31, 2016 as a result of our follow-on offering of common stock, which closed in August 2015; and (3) $23 thousand of realized gains on sales of marketable securities.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception and through December 31, 2017, we have raised an aggregate of approximately $324.5 million to fund our operations, including (1) net proceeds of $217.7 million from the sale of shares of our common stock in three 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; and (3) payments of $33.5 million under our license agreements, primarily with Maruishi and CKDP, and an earlier product candidate for which development efforts ceased in 2007.

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 gross proceeds from the offering of approximately $92.1 million, or 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 being used to fund our clinical and research development activities, including the completion of the Phase 3 program for I.V. KORSUVA (CR845/difelikefalin) in uremic pruritus, additional trials of Oral CR845/difelikefalin in other diseases associated with pruritus, the Phase 2/3 I.V. CR845/difelikefalin adaptive clinical trial in postoperative pain, as well as for working capital and 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, 2017, we had $92.6 million in unrestricted cash and cash equivalents and available-for-sale marketable securities, which we believe will be sufficient to fund our currently anticipated operating expenses and capital expenditures into the first half of 2019, without giving effect to any potential milestone payments we may receive under our collaboration agreements with Maruishi and CKDP.

In addition, under the Maruishi Agreement, we are 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.

During the second quarter of 2014, Maruishi completed a Phase 1 clinical trial in Japan related to CR845/difelikefalin in acute post-operative pain for which we earned a clinical development milestone payment of $480 thousand, net of contractual foreign currency exchange adjustments of $20 thousand. During the third quarter of 2015, Maruishi initiated a Phase 2 trial in Japan related to CR845/difelikefalin for the treatment of uremic pruritus for which we earned a clinical development milestone payment of $1.7 million, net of contractual foreign currency exchange adjustments of $275 thousand. 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.

The next potential milestones that we could be entitled to receive under the Maruishi Agreement will be a clinical development milestone for the completion by us of the first Phase 3 trial of CR845/difelikefalin in acute pain in the United States and the initiation by Maruishi of a Phase 3 clinical trial of CR845/difelikefalin in Japan for uremic pruritus. If achieved, these milestones will result in payments of $1.0 million and $2.0 million, respectively, before contractual foreign currency exchange adjustments, being due to us.

Under the CKDP Agreement, we are potentially eligible to earn up to an aggregate of $2.25 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.

During 2012 and 2015, we earned a total of $1.25 million, net of South Korean withholding tax of $0.25 million, related to four milestones involving clinical trials in the United States of CR845/difelikefalin in acute post-operative pain and for the treatment of uremic pruritus.

The next potential milestone payment that we could be entitled to receive 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 $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, clinical costs, legal and other regulatory expenses and general overhead 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 $58.1 million, $57.3 million and $24.7 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $220.3 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 collaborations with Maruishi and CKDP, the receipt of payments under any future collaborations 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;
- continue the development of Oral KORSUVA (CR845/difelikefalin) for CKD-aP and other diseases associated with pruritus;
- continue our I.V. CR845/difelikefalin clinical trial program in acute pain;
- continue the 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 product candidates. 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 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 collaboration agreements with 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, conducting Phase 1 and Phase 2 trials of Oral (CR845/difelikefalin) in patients with CKD-aP and CLD-aP and completing required trials for I.V. CR845/difelikefalin in postoperative pain to enable an NDA submission; we expect that our existing cash and cash equivalents and available-for-sale marketable securities as of December 31, 2017 will be sufficient for us to fund our operating expenses and capital expenditure requirements into the first half of 2019, without giving effect to any potential milestone payments we may receive under our collaboration agreements with Maruishi and CKDP. 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.

ASC 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 NOL's, 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. NOL's 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, 2017, 2016 and 2015:

	Year Ended December 31,		
	2017	2016	2015
	Amounts in thousands		
Net cash used in operating activities	$ (54,827)	$ (47,381)	$ (21,478)
Net cash (used in) provided by investing activities	(35,800)	44,249	(91,677)
Net cash provided by financing activities	87,923	123	75,593
Net decrease in cash and cash equivalents	$ (2,704)	$ (3,009)	$ (37,562)

Net cash used in operating activities

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 (including $0.5 million related to modification of equity awards) 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 operating activities for the year ended December 31, 2015 consisted primarily of a net loss of $24.7 million, a $0.2 million inflow from net changes in operating assets and liabilities and a $3.0 million cash inflow from net non-cash charges. Net non-cash charges primarily consisted of depreciation and amortization expense of $0.8 million and stock-based compensation expense of $2.5 million, partially offset by deferred rent costs of $0.3 million. The net change in operating assets and liabilities primarily consisted of cash outflows from a $1.5 million decrease in deferred revenue, in connection with the completion of our obligation to deliver R&D services to Maruishi in 2015 under the Maruishi Agreement, a $1.4 million increase in prepaid expenses, primarily related to increases in prepaid clinical costs and an increase in income tax receivable of $0.2 million. Those cash outflows were partially offset by a cash inflow from a $3.3 million increase in accounts payable and accrued expenses.

Net cash (used in) provided by investing activities

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, $8.8 million from the sale of available-for-sale securities and $0.7 million from a decrease in restricted cash.

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, $0.7 million of cash paid for purchase of property and equipment and $0.8 million of additional restricted cash related to our Stamford lease.

Net cash used in investing activities for the year ended December 31, 2015, primarily included a cash outflow of $91.7 million related to the purchase of available-for-sale marketable securities.

Net cash provided by financing activities

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.

Net cash provided by financing activities for the year ended December 31, 2015 consisted primarily of gross proceeds of $80.5 million from our follow-on offering of common stock, partially offset by $5.3 million of underwriting discounts and commissions and offering expenses paid by us during the year ended December 31, 2015, and proceeds of $0.4 million received from stock option exercises.

Contractual Obligations

The following table summarizes our significant contractual obligations as of December 31, 2017 (in thousands):

	Payment Due for the Year Ending December 31,						
	2018	2019	2020	2021	2022	Thereafter	Total
Stamford operating lease	$ 1,091	$ 1,215	$ 1,240	$ 1,264	$ 1,288	$ 1,164	$ 7,262

See Note 16 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

In general, we recognize revenue when all of the following criteria are met: persuasive evidence of an arrangement exists; our price to the customer is fixed or determinable; collectability is reasonably assured and delivery has occurred or services have been rendered.

We have entered into license agreements to develop, manufacture and commercialize drug products. The terms of these agreements typically contain multiple elements, including licenses and R&D services. Payments to us under these agreements may include non-refundable upfront license fees, payments for research activities, payments based upon the achievement of certain clinical development and regulatory milestones and royalties on any resulting net product sales. There are no performance, cancellation, termination or refund provisions in any of the arrangements that contain material financial consequences to us.

We record revenue related to these agreements in accordance with Accounting Standards Codification or ASC, 605-25, *Revenue Recognition Multiple-Element Arrangements*. In order to account for these agreements, we identify the deliverables included within an arrangement and evaluate which deliverables represent separate units of accounting based on whether certain criteria are met, including whether the delivered element has standalone value to the counterparty. The consideration received is then allocated among the separate units of accounting based on each unit's relative selling price.

The identification of individual elements in a multiple-element arrangement and the estimation of the selling price of each element involves significant judgment, including consideration as to whether each delivered element has standalone value. We have determined that our license deliverables represent separate units of accounting because the counterparty has the right to sublicense and manufacture in its territory, as defined. We have determined that our R&D services deliverables, as applicable, represent separate units of accounting because similar services are sold separately by other vendors.

We determine the estimated selling price for deliverables within each agreement using vendor specific objective evidence, or VSOE, of selling price, if available, or third-party evidence, or TPE, of selling price if VSOE is not available, or our best estimate of selling price, if neither VSOE nor TPE is available. Determining the best estimate of selling price for a deliverable requires significant judgment. Because we do not have VSOE or TPE of selling price to determine the estimated selling price of a license to our proprietary technology, we typically use our best estimate of a selling price to estimate the selling prices for licenses to our proprietary technology. In making these estimates, we consider market conditions and entity-specific factors, including those contemplated in negotiating the agreements, as well as internally developed estimates that include assumptions related to the market opportunity, estimated development costs, probability of success and the time needed to commercialize a product candidate pursuant to the license. In validating our best estimate of selling price, we evaluate whether changes in the key assumptions used to determine our best estimate of selling price will have a significant effect on the allocation of arrangement consideration between deliverables. We recognize consideration allocated to an individual element when all other revenue recognition criteria are met for that element.

Arrangement consideration allocated to license deliverables that represent separate units of accounting are recognized as revenue at the outset of the agreement assuming the general criteria for revenue recognition noted above have been met. Arrangement consideration allocated to license deliverables which do not represent separate units of accounting are deferred. Arrangement consideration allocated to R&D services which represent separate units of accounting are recognized as the services are performed, assuming the general criteria for revenue recognition noted above have been met.

In connection with arrangement consideration allocated to R&D services, our performance period estimates are principally based on projections of the scope, progress and results of our R&D activities. Due to the variability in the scope of activities and length of time necessary to develop a drug product, changes to development plans as programs progress, and uncertainty in the ultimate requirements to obtain governmental approval for commercialization, revisions to performance period estimates are likely to occur periodically, and could result in material changes to the amount of revenue recognized each year in the future. In addition, our estimated performance periods may change if development programs encounter delays or we decide to expand or contract our clinical plans for a drug candidate.

Our license agreements include contingent milestone payments related to specified clinical development milestones and regulatory milestones. Development milestones are payable when a product candidate initiates or advances into different clinical trial phases. Regulatory milestones are payable upon submission for marketing approval with the FDA or other countries' regulatory authorities or on receipt of actual marketing approvals for the compound or for additional indications. At the inception of each agreement that includes milestone payments, we evaluate whether each such payment is a milestone payment as defined by ASC 605-28, *Revenue Recognition – Milestone Method*, because achievement requires performance by us and, at inception of the arrangement, there is substantive uncertainty that the event will be achieved, or whether the payment is a contingent payment, because achievement requires performance by the counterparty.

If the payment meets the criteria of a milestone payment, we evaluate whether such milestone is considered to be substantive. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (b) the consideration relates solely to past performance and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. We evaluate factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment.

We recognize substantive milestone payments as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If any milestone payment is considered not to be a substantive milestone or if considered to be a contingent payment, we initially defer the milestone payment, allocate it to the deliverables based on relative selling price in the same proportion as at inception of the agreement, immediately recognize revenue to the extent of any delivered elements and recognize the portion attributable to any undelivered elements over the remaining term of our performance obligations. If no such performance obligations exist, milestones that are considered not to be substantive or are considered to be contingent payments are generally recognized as revenue upon achievement, assuming all other revenue recognition criteria are met.

Royalty revenue is recognized when earned. To date, no royalties have been earned or were otherwise due to us.

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, 2017, 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 75% - 85% and 68% - 78% during the years ended December 31, 2017 and 2016, respectively. The actual volatility of our common stock from January 31, 2014 to December 31, 2017 and 2016 was 79% and 78%, 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*, and account for forfeitures as they occur from that date (see *Accounting Pronouncements Recently Adopted*, below).

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.

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 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 320-10-20 and has a maturity at the time of purchase of more than three months. 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, 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, 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 on our Balance Sheets 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, 2017, 2016 or 2015.

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 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, 2017, or 2016. 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

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, salaries and other personnel-related costs, including consultant costs, and costs to conduct clinical trials using 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 and facility-related costs. 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.

Leases

In December 2015, we entered into a lease agreement, or the Stamford Lease, with Four Stamford Plaza Owner LLC, or the Landlord, for office space in Stamford, Connecticut, or the Premises, for the purpose of relocating our 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, totaling $8.4 million, including rent escalations and rent holidays, during the initial lease term. We began to make rental payments from the Commencement Date. We record monthly rent expense on a straight-line basis from March 2016, upon taking possession of the Premises, through October 2023. The Stamford Lease is renewable for one five-year term. See Note 16 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K for further information about the Stamford Lease.

The Stamford landlord has made tenant improvements to the leased premises, the amount of which was included in Property and equipment, net and in Deferred lease obligation on our Balance Sheet on the Commencement Date. 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.

We recognize rent expense for operating leases on a straight-line basis over the term of the lease, beginning on the date we take 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, we determine 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 our 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 lease obligation and classified within long-term liabilities on the Balance Sheets. Lease incentives made by landlords to us, or on our behalf, 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.

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.

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107(b) of the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably

elected not to avail ourselves of this extended transition period, and, as a result, we have been adopting, and will continue to adopt, new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

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 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, 2017, we had 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 interest rate of 1.32%. As of December 31, 2016, we have invested $46.2 million of our cash reserves in such marketable securities. Those marketable securities include $37.9 million of investment grade debt instruments with an average interest rate of approximately 1.0% and maturities through August 2017 and $8.3 million of money market funds with an average interest rate of 0.92%.

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, 2017, and 2016, 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, 2017. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2017, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC, and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosures.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management utilized the criteria established in the Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) to conduct an assessment of the effectiveness of our internal control over financial reporting as of December 31, 2017. Based on the assessment, management has concluded that, as of December 31, 2017, 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(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2017 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 information required by this item will be set forth under the captions "Executive Officers and Directors of Cara", "Director Nomination Process", "Information Regarding the Board of Directors and its Committees – Audit Committee", "Section 16(a) Beneficial Ownership Reporting Compliance" and "Code of Ethics and Business Conduct" in our Definitive Proxy Statement with respect to our 2018 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. ***Executive Compensation.***

The information required by this item will be set forth under the captions "Compensation of Named Executive Officers", "Director Compensation" and "Compensation Committee Interlocks and Insider Participation" in our Definitive Proxy Statement with respect to our 2018 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this item will be set forth under the captions "Security Ownership of Certain Beneficial Owners and Management" and "Securities Authorized for Issuance under Equity Compensation Plans" in our Definitive Proxy Statement with respect to our 2018 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this item will be set forth under the captions "Transactions with Related Persons" and "Independence of the Board of Directors" in our Definitive Proxy Statement with respect to our 2018 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. ***Principal Accountant Fees and Services.***

The information required by this item will be set forth under the caption "Independent Registered Public Accounting Firm's Fees" in our Definitive Proxy Statement with respect to our 2018 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. ***Exhibits, Financial Statement Schedules.***

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

	PAGE
Report of Independent Registered Public Accounting Firm	F-1
Balance Sheets as of December 31, 2017 and 2016	F-2
Statements of Comprehensive Loss for the years ended December 31, 2017, 2016 and 2015	F-3
Statements of Stockholders' Equity for the years ended December 31, 2017, 2016 and 2015	F-4
Statements of Cash Flows for the years ended December 31, 2017, 2016 and 2015	F-5
Notes to Financial Statements	F-6

(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+[10]	Services Agreement dated July 2, 2004 between the Registrant and Bio Diligence Partners, Inc., including amendments 1 -10.
10.4.1+ [11]	Eleventh amendment to Services Agreement dated July 2, 2004 between the Registrant and Bio Diligence Partners, Inc.
10.4.2+ [12]	Twelfth amendment to Services Agreement dated July 2, 2004 between the Registrant and Bio Diligence Partners, Inc.
10.5[4]	Fourth Amended and Restated Investors Rights Agreement dated April 25, 2013 among the Registrant and certain of its stockholders, as amended.
10.6[4]	Lease Agreement dated September 18, 2006 between the Registrant and Shelton Parrott Associates, L.L.C., as amended.
10.7*[4]	License Agreement dated April 4, 2013 by and between the Registrant and Maruishi Pharmaceutical Co., Ltd.
10.8*[4]	License and API Supply Agreement effective as of April 16, 2012 by and between the Registrant and Chong Kun Dang Pharmaceutical Corp.
10.9[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.
10.10+[5]	Employment Agreement with Derek Chalmers.
10.11+[6]	Employment Agreement with Frédérique Menzaghi.
10.12+[7]	Employment Agreement with Josef Schoell.
10.13+[3]	Non-Employee Director Compensation Policy.
10.14 +[8]	Employment 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 [13]	Employment Agreement with Mani Mohindru, Ph.D.
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.

Exhibit No.	Description of Exhibit
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.

† 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 Quarterly Report on Form 10-Q (File No. 001-36279) filed with the Securities and Exchange Commission on August 10, 2015 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 4, 2016 and incorporated herein by reference.

(12) 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 November 4, 2016 and incorporated herein by reference.

(13) 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.

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 15th day of March 2018.

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 15, 2018
/s/ MANI MOHINDRU Mani Mohindru, Ph.D.	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 15, 2018
/s/ HARRISON BAINS Harrison Bains	Director	March 15, 2018
/s/ JEFFREY IVES Jeffrey Ives, Ph.D.	Director	March 15, 2018
/s/ MARTIN VOGELBAUM Martin Vogelbaum	Director	March 15, 2018

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, 2017 and 2016, and the related statements of comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2017, 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, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with US 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 15, 2018

CARA THERAPEUTICS, INC.

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

	December 31, 2017	December 31, 2016
Assets		
Current assets:		
Cash and cash equivalents	$ 9,388	$ 12,092
Marketable securities	83,181	46,184
Income tax receivable	731	852
Other receivables	123	87
Prepaid expenses	1,635	1,530
Restricted cash, current	—	700
Total current assets	95,058	61,445
Property and equipment, net	1,177	1,614
Restricted cash	769	769
Total assets	$ 97,004	$ 63,828
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 8,506	$ 11,533
Total current liabilities	8,506	11,533
Deferred lease obligation	1,718	1,570
Commitments and contingencies (Note 16)	—	—
Stockholders' equity:		
Preferred stock; $0.001 par value; 5,000,000 shares authorized at December 31, 2017 and December 31, 2016; zero shares issued and outstanding at December 31, 2017 and December 31, 2016	—	—
Common stock; $0.001 par value; 100,000,000 shares authorized at December 31, 2017 and December 31, 2016; 32,662,255 shares and 27,296,863 shares issued and outstanding at December 31, 2017 and December 31, 2016, respectively	33	27
Additional paid-in capital	307,158	212,866
Accumulated deficit	(220,341)	(162,171)
Accumulated other comprehensive (loss) income	(70)	3
Total stockholders' equity	86,780	50,725
Total liabilities and stockholders' equity	$ 97,004	$ 63,828

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,		
	2017	2016	2015
Revenue:			
License and milestone fees	$ 530	$ —	$ 1,710
Collaborative revenue	313	—	2,093
Clinical compound revenue	68	86	—
Total revenue	911	86	3,803
Operating expenses:			
Research and development	48,524	49,253	21,221
General and administrative	11,872	9,233	7,770
Total operating expenses	60,396	58,486	28,991
Operating loss	(59,485)	(58,400)	(25,188)
Other income	1,156	652	101
Loss before benefit from income taxes	(58,329)	(57,748)	(25,087)
Benefit from income taxes	204	468	397
Net loss	$ (58,125)	$ (57,280)	$ (24,690)
Net loss per share:			
Basic and Diluted	$ (1.86)	$ (2.10)	$ (1.00)
Weighted average shares:			
Basic and Diluted	31,202,842	27,279,008	24,620,372
Other comprehensive income (loss), net of tax of $0:			
Change in unrealized gains (losses) on available for sale marketable securities	(73)	38	(35)
Total comprehensive loss	$ (58,198)	$ (57,242)	$ (24,725)

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	Total Stockholders'
	Shares	Amount	Capital	Deficit	Income (Loss)	Equity
Balance at December 31, 2014	22,802,039	$ 23	$ 131,840	$ (80,201)	$ —	$ 51,662
Sale of common stock in a follow-on public offering ($18.60 per share), net of underwriting discounts and commissions and offering expenses of $5,269	4,327,956	4	75,227	—	—	75,231
Stock-based compensation expense	—	—	2,514	—	—	2,514
Shares issued upon exercise of stock options	124,868	—	362	—	—	362
Net loss	—	—	—	(24,690)	—	(24,690)
Other comprehensive loss	—	—	—	—	(35)	(35)
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

See Notes to Financial Statements.

CARA THERAPEUTICS, INC.

STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,		
	2017	**2016**	**2015**
Operating activities			
Net loss	$ (58,125)	$ (57,280)	$ (24,690)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	5,793	2,800	2,514
Modification of equity awards	537	—	—
Depreciation & amortization	495	1,465	839
Amortization/accretion of available-for-sale marketable securities	(582)	(218)	(18)
Realized gain on sale of available-for-sale marketable securities	(5)	(23)	—
Realized gain on sale of property and equipment	(41)	—	—
Deferred rent costs	148	(114)	(289)
Loss on write-off of fixed assets	—	—	2
Changes in operating assets and liabilities:			
Income tax receivable	121	(468)	(184)
Other receivables	(36)	(7)	(80)
Prepaid expenses	(105)	199	(1,442)
Accounts payable and accrued expenses	(3,027)	6,265	3,322
Deferred revenue	—	—	(1,452)
Net cash used in operating activities	(54,827)	(47,381)	(21,478)
Investing activities			
Proceeds from maturities of available-for-sale marketable securities	82,156	80,380	—
Proceeds from sale of available-for-sale marketable securities	8,755	34,003	—
Purchase of available-for-sale marketable securities	(127,394)	(68,648)	(91,657)
Change in restricted cash	700	(769)	—
Purchases of property and equipment	(58)	(717)	(20)
Proceeds from sale of property and equipment	41	—	—
Net cash (used in) provided by investing activities	(35,800)	44,249	(91,677)
Financing activities			
Proceeds from follow-on offering, net of issuance costs	86,224	—	75,231
Proceeds from the exercise of stock options	1,699	123	362
Net cash provided by financing activities	87,923	123	75,593
Net cash decrease for the period	(2,704)	(3,009)	(37,562)
Cash and cash equivalents at beginning of period	12,092	15,101	52,663
Cash and cash equivalents at end of period	$ 9,388	$ 12,092	$ 15,101
Noncash financing activities			
Tenant improvements paid by landlord	$ —	$ 1,094	$ —

See Notes to Financial Statements.

1. Business

Cara Therapeutics, Inc., or the Company, is a clinical-stage biopharmaceutical corporation formed on July 2, 2004. The Company is focused on developing and commercializing new chemical entities designed to alleviate pruritus and pain by selectively targeting 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, 2017, the Company has raised aggregate net proceeds of approximately $291,100 from several rounds of equity financing, including its initial public offering, or IPO, which closed in February 2014 and two follow-on public offerings of common stock, which closed in April 2017 and August 2015, respectively, and the issuance of convertible preferred stock and debt prior to the IPO. In addition, the Company received approximately $33,500 under its license agreements for CR845/difelikefalin, primarily with 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 (see Note 11, *Collaborations*).

On April 5, 2017, the Company completed its second follow-on public offering, raising aggregate proceeds of approximately $86,224, net of underwriting discounts and commissions and offering expenses paid by the Company. The offering was conducted pursuant to a shelf registration statement on Form S-3, which was filed on March 13, 2017 and declared effective by the Securities and Exchange Commission, or the SEC, on March 24, 2017 (see Note 9, *Stockholders' Equity*).

As of December 31, 2017, the Company had unrestricted cash and cash equivalents and marketable securities of $92,569 and an accumulated deficit of $220,341. 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 $58,125 and had net cash used in operating activities of $54,827 for the year ended December 31, 2017.

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

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. Significant 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 two 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 and has a maturity at the time of purchase of more than three months. 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 generally 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 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.

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, *Marketable Securities*, and Note 10, *Fair Value Measurement*.

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, 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 on the Company's Balance Sheets 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.

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

Valuation Techniques - Level 2 Inputs

The Company estimates the fair values of its financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, commercial paper 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, 2016 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
Laboratory equipment	8 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)

Long-Lived Assets

ASC 360, *Property, Plant and Equipment*, addresses the financial accounting and reporting for impairment or disposal of long-lived assets. The Company reviews the recorded values of long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of an asset or group of assets may not be fully recoverable.

Revenue Recognition

In general, the Company recognizes revenue when all of the following criteria are met: persuasive evidence of an arrangement exists; the Company's price to the customer is fixed or determinable; collectability is reasonably assured and delivery has occurred or services have been rendered.

The Company has entered into license agreements to develop, manufacture and commercialize drug products. The terms of these agreements typically contain multiple elements, including licenses 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. There are no performance, cancellation, termination or refund provisions in any of the arrangements that contain material financial consequences to the Company.

The Company records revenue related to these agreements in accordance with ASC 605-25, *Revenue Recognition Multiple-Element Arrangements*. In order to account for these agreements, the Company identifies the deliverables included within an arrangement and evaluates which deliverables represent separate units of accounting based on whether certain criteria are met, including whether the delivered element has standalone value to the counterparty. The consideration received is then allocated among the separate units of accounting based on each unit's relative selling price.

The identification of individual elements in a multiple-element arrangement and the estimation of the selling price of each element involves significant judgment, including evaluation as to whether each delivered element has standalone value. The Company has determined that its license deliverables represent separate units of accounting because the counterparty has the right to sublicense and manufacture in its territory, as defined. The Company has determined that its R&D services deliverables, as applicable, represent separate units of accounting because similar services are sold separately by other vendors.

The Company determines the estimated selling price for deliverables within each agreement using vendor specific objective evidence, or VSOE, of selling price, if available, or third-party evidence, or TPE, of selling price if VSOE is not available, or the Company's best estimate of selling price, if neither VSOE nor TPE is available. Determining the best estimate of selling price for a deliverable requires significant judgment. Because the Company does not have VSOE or third-party evidence of selling price to determine the estimated selling price of a license to its proprietary technology, it typically uses its best estimate of a selling price to estimate the selling prices for licenses to its proprietary technology. In making these estimates, the Company considers market conditions and entity-specific factors, including those contemplated in negotiating the agreements, as well as internally developed estimates that include assumptions related to the market opportunity, estimated development costs, probability of success and the time needed to commercialize a product candidate pursuant to the license. In validating its best estimate of selling price, the Company evaluates whether changes in the key assumptions used to determine its best estimate of selling price will have a significant effect on the allocation of arrangement consideration between deliverables. The Company recognizes consideration allocated to an individual element when all other revenue recognition criteria are met for that element.

Arrangement consideration allocated to license deliverables that represent separate units of accounting is recognized as revenue at the outset of the agreement assuming the general criteria for revenue recognition noted above have been met. Arrangement consideration allocated to license deliverables which do not represent separate units of accounting is deferred. Arrangement consideration allocated to R&D services which represent separate units of accounting is recognized as the services are performed, assuming the general criteria for revenue recognition noted above have been met.

The Company's license agreements include contingent milestone payments related to specified clinical development milestones and regulatory milestones. Development milestones are payable when a product candidate initiates or advances into different clinical trial phases. Regulatory milestones are payable upon submission for marketing approval with the FDA or other countries' regulatory authorities or on receipt of actual marketing approvals for the compound or for additional indications. At the inception of each agreement that includes milestone payments, the Company evaluates whether each such payment is a milestone payment as defined by ASC 605-28, *Revenue Recognition – Milestone Method*, because achievement requires performance by the Company and, at inception of the arrangement, there is substantive uncertainty that the event will be achieved, or whether the payment is a contingent payment, because achievement requires performance by the counterparty.

If the payment meets the criteria of a milestone payment, the Company evaluates whether such milestone is considered to be substantive. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (b) the consideration relates solely to past performance and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment.

The Company recognizes substantive milestone payments as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If any milestone payment is considered not to be a substantive milestone or is considered to be a contingent payment, the Company initially defers the milestone payment, allocates it to the deliverables based on relative selling price in the same proportion as at inception of the agreement, immediately recognizes revenue to the extent of any delivered elements and recognizes the portion attributable to any undelivered elements over the remaining term of its performance obligations. If no such performance obligations exist, milestones that are considered not to be substantive or are considered to be contingent payments are generally recognized as revenue upon achievement, assuming all other revenue recognition criteria are met.

Royalty revenue is recognized when earned. To date, no royalties have been earned or were otherwise due to the Company.

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, salaries 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 and facility-related costs. 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, 2017 and 2016, the Company recorded $1,287 and $1,256 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. The financial statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. There were no material uncertain tax positions taken as of December 31, 2017 and December 31, 2016. 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 in the Statements of Comprehensive Loss based on their grant date fair values. The grant date fair value of stock options is estimated using the Black-Scholes option valuation model.

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

The Company's common stock has been traded on a public exchange only since January 31, 2014. Since that time, exercises of stock options have been limited due to various factors, including fluctuations in the Company's stock price to below the exercise prices of awards and blackout periods during which exercises are not allowed, among others. Therefore, the Company believes that as of December 31, 2017, 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. 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 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 Accounting Standards Update, or ASU, 2016-09, *Improvements to Employee Share-Based Payment Accounting*, and accounts for forfeitures as they occur from that date (see *Accounting Pronouncements Recently Adopted*, below).

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 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. 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. Compensation cost relating to awards with service-based graded vesting schedules is recognized using the straight-line method.

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, 2017, 2016 and 2015, 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.

Litigation Reserves

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

Accounting Pronouncements Recently Adopted

As of January 1, 2017, the Company adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting*, or ASU 2016-09, which amends ASC Topic 718, *Compensation – Stock Compensation*. ASU 2016-09 simplifies several aspects of the accounting for share-based payment transactions, including the accounting for forfeitures, income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. Certain of the amendments were applied using a modified retrospective transition method by means of a cumulative-effect adjustment to equity as of January 1, 2017, while other amendments were applied retrospectively, prospectively or using either a prospective or a retrospective transition method. Upon adoption, the Company began to account for forfeitures as they occur rather than estimate forfeiture rates for stock option awards. As a result, the Company recorded a cumulative-effect adjustment to stockholders' equity of $45 on the date of initial adoption for all stock option awards that were unvested as of that date. In periods subsequent to adoption, a higher expense will be recognized earlier during the respective vesting periods of stock-based awards that are not forfeited. The Company expects that the income tax amendments within ASU 2016-09 will have no impact on its results of operations or cash flows because it is in a net operating loss position with a full valuation allowance against its deferred tax assets.

Recent Accounting Pronouncements Not Yet Adopted

In May 2017, the Financial Accounting Standards Board, or FASB, issued 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. ASU 2017-09 is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2017. The Company generally has not modified, and does not expect to frequently modify, the fair value, vesting conditions or classification of its share-based payment awards. As a result, for reporting periods following the adoption of ASU 2017-09, the Company generally 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 (see Note 12, *Stock-based Compensation*).

In January 2017, the FASB issued 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. ASU 2017-01 will be applied prospectively and is effective for annual periods beginning after December 15, 2017 and interim periods within those annual periods. The Company does not expect that the adoption of ASU 2017-01 will have a material effect on its financial position, results of operations or cash flows since it has not and does not expect to acquire or dispose of assets for which the fair value is divided among diverse identifiable assets.

In December 2016, the FASB issued ASU No. 2016-20, *Technical Corrections and Improvements to Topic 606, Revenue from Contracts with Customers,* or ASU 2016-20, that allows entities not to disclose variable consideration allocated to performance obligations related to either: (1) sales - or usage -based royalties on licenses of intellectual property or (2) variable consideration allocated entirely to a wholly unsatisfied performance obligation or to a wholly unsatisfied promise to transfer a distinct good or service that forms part of a single performance obligation when certain criteria are met. ASU 2016-20 also requires entities that use any of the new or previously existing optional exemptions to expand their qualitative disclosures. It also makes 12 additional technical corrections and improvements to the new revenue standard, ASU 2014-09. The amendments have the same effective date and transition requirements as ASU 2014-09. The Company does not expect the adoption of ASU 2016-20 to have a material effect on its financial position, results of operations or cash flows.

In November, 2016, the FASB issued 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. ASU 2016-18 will be applied retrospectively to all periods presented and is effective for public business entities for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. The Company currently presents changes in restricted cash as an investing activity in the statement of cash flows. Upon adoption of ASU 2016-18, such changes will be reflected in the beginning and ending balances of cash, cash equivalents and restricted cash for all periods presented.

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. The Company is currently evaluating the effect that adoption of ASU 2016-13 will have on its results of operations, financial position and cash flows.

In May 2016, the FASB issued ASU No. 2016-12*, Revenue from Contracts with Customers (Topic 606), Narrow-Scope Improvements and Practical Expedients*, or ASU 2016-12, which amends guidance in the new revenue standard, ASU No. 2014-09 *Revenue from Contracts with Customers (Topic 606)*, or ASU 2014-09, on collectability, noncash consideration, presentation of sales tax and transition. The amendments in ASU 2016-12 are effective for annual reporting periods beginning after December 15, 2017 (i.e., January 1, 2018), including interim periods within those reporting periods, which is the same as for ASU 2014-09, as amended by ASU No. 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, or ASU 2015-14. See ASU 2014-09, below, for a discussion of the effect that adoption of ASU 2016-12 is expected to have on the Company's financial statements.

In April 2016, the FASB issued ASU No. 2016-10, *Revenue from Contracts with Customers (Topic 606), Identifying Performance Obligations and Licensing*, or ASU 2016-10*,* which clarifies the principle for determining whether a good or service is "separately identifiable" from other promises in the contract and, therefore, should be accounted for as a separate performance obligation. In that regard, ASU 2016-10 requires that an entity determine whether its promise is to transfer individual goods or services to the customer, or a combined item (or items) to which the individual goods and services are inputs. In addition, ASU 2016-10 categorizes intellectual property, or IP, into two categories: "functional" and "symbolic." Functional IP has significant standalone functionality. All other IP is considered symbolic IP. Revenue from licenses of functional IP is generally recognized at a point in time, while revenue from licenses of symbolic IP is recognized over time. ASU 2016-10 has the same effective date and transition requirements as ASU 2014-09, as amended by ASU 2015-14. See ASU 2014-09, below, for a discussion of the effect that adoption of ASU 2016-10 is expected to have on the Company's financial statements.

In March 2016, the FASB issued ASU No. 2016-08, *Revenue from Contracts with Customers (Topic 606), Principal versus Agent Considerations (Reporting Revenue Gross versus Net)*, or ASU 2016-08, which clarifies the implementation guidance on principal versus agent considerations contained in ASU 2014-09 by specifying that the determination as to whether an entity that is involved in providing a good or a service to a customer is a principal or an agent is based upon whether the entity controls the good or the service before it is transferred to the customer. ASU 2016-08 has the same effective date and transition requirements as ASU 2014-09, as amended by ASU 2015-14. See ASU 2014-09, below, for a discussion of the effect that adoption of ASU 2016-08 is expected to have on the Company's financial statements.

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. ASU 2016-02 requires a lessee to recognize in its balance sheet a liability to make lease payments and a right-of-use asset representing its right to use the underlying asset for the lease term. The lease liability will be equal to the present value of lease payments and the right-of-use asset will be based on the lease liability, subject to adjustment such as for initial direct costs. For income statement purposes, the new standard retains a dual model similar to ASC 840, requiring leases to be classified as either operating leases or capital leases. For lessees, operating leases will result in straight-line expense (similar to current accounting by lessees for operating leases under ASC 840) while capital leases will result in a front-loaded expense pattern (similar to current accounting by lessees for capital leases under ASC 840). ASU 2016-02 requires a lessee to disclose qualitative and quantitative information about its leasing arrangements. 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 has approved an amendment to ASU 2016-02, which allows entities to elect to continue 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 option would record the cumulative effect of adoption on the effective date rather than at the beginning of the earliest comparative period presented. The Company is continuing to evaluate the impact that ASU 2016-02 will have on its financial statements.

In May 2014, the FASB issued ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)*, or ASU 2014-09, which changes the principle under which the Company will recognize revenue from contracts with customers from one which requires the Company to satisfy specific criteria before recognizing revenue to one which requires the Company to recognize 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. ASU 2014-09, as amended, defines

a five-step process to achieve this core principle: (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.

During the years ended December 31, 2017, 2016 and 2015, the Company recognized revenue only from a license agreement with Maruishi, or the Maruishi Agreement, and a license agreement with CKDP, or the CKDP Agreement. Under each of these agreements, the Company has recognized revenue from upfront and milestone payments and may earn additional future milestone payments upon the achievement of defined clinical development and regulatory events. The Company has also recognized revenue from a sub-license fee under the Maruishi Agreement. Since all defined milestones will not have been achieved and the related revenue will not have been recognized under ASC 605 as of the date of adoption of ASU 2014-09, as amended, those contracts will be included within the scope of ASU 2014-09, as amended.

The Company is currently accounting for the Maruishi Agreement and the CKDP Agreement under ASC 605-25, *Multiple-Element Arrangements* and ASC 605-28, *Milestone Method*. The Company has analyzed the terms and conditions of each of these contracts in light of the guidance under ASU 2014-09, including amendments under ASU 2016-08, 2016-10, 2016-12 and 2016-20, and has concluded that, due to the similarity of the application of the guidance under ASC 605-25 and ASC 605-28 and under ASU 2014-09, as amended, as it relates to revenue recognition for licenses of intellectual property, or IP, as applied to each of these contracts, the distinct performance obligations, transaction prices, amount of the transaction price allocated to the performance obligations and timing and amount of revenue recognition under ASU 2014-09, as amended, will be the same as under ASC 605-25 and ASC 605-28.

In particular, the following aspects of ASU 2014-09, as amended, are the same as those under ASC 605-25 and ASC 605-28 in respect of the Maruishi Agreement and the CKDP Agreement. The Maruishi Agreement has two distinct performance obligations, granting of the license and the R&D services and the CKDP Agreement has one distinct performance obligation, granting of the license. The methodology for determining the relative standalone selling price of the performance obligations and the allocation of the transaction price to the performance obligations is the same under both standards. The licenses granted to the counterparties under these two contracts are deemed to be functional IP for which revenue is recognized at a point in time, which has been determined to be inception of the respective license agreements, the same as under ASC 605. The R&D services under the Maruishi Agreement were performed from inception of the agreement in 2013 through the third quarter of 2015. Accordingly, under ASU 2014-09, as amended, revenue related to the R&D services under the Maruishi Agreement would be recognized proportionately as those services were performed, as it was under ASC 605-25.

Although the milestone method guidance under ASC 605-28 no longer applies under ASU 2014-09, as amended, the guidance under ASU 2014-09, as amended, for milestones and sales-based royalties related to licenses of IP is effectively the same as pertains to milestones achieved by the Company and those achieved by the counterparty to each license agreement. In addition, due to the probability, at inception of each of the two license agreements, that revenue recognized related to the achievement of milestones and sales-based royalty payments will be reversed in the future, the constraint on including those potential payments in the transaction price at that time applies under ASU 2014-09, as amended. Under ASU 2014-09, as amended, recognition of revenue for achievement of any milestone and sales-based royalty payment will occur at the time that it becomes probable that those events will be achieved. Application of the guidance under ASU 2014-09, as amended, to the milestones achieved under the Maruishi Agreement and the CKDP Agreement prior to adoption of that standard will not change the amount or timing of revenue recognized under ASC 605 for any reporting period presented at or after the date of adoption of ASU 2014-09, as amended. As a result of the foregoing considerations, the Company has concluded that upon adoption of ASU 2014-09, as amended, there will be no impact on its results of operations, financial position or cash flows for any period presented from the CKDP Agreement or the Maruishi Agreement.

ASU 2014-09, as amended by ASU 2015-14, is effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual reporting periods. ASU 2014-09, as amended, allows for two transition methods: (1) retrospectively to each prior reporting period presented, or (2) using a modified

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

retrospective approach, with the cumulative effect of initially applying ASU 2014-09, as amended, recognized as an adjustment to the opening balance of retained earnings at the date of initial adoption. The Company adopted ASU 2014-09, as amended, using the full retrospective method on January 1, 2018.

3. Available-for-Sale Marketable Securities

As of December 31, 2017, and 2016, the Company's available-for-sale marketable securities consisted of money market funds and debt securities issued by U.S. government-sponsored entities and by investment grade institutions. As of December 31, 2016, the Company's available-for-sale marketable securities also included debt securities issued by the U.S. Treasury.

The following tables summarize the Company's available-for-sale marketable securities by major type of security as of December 31, 2017, and 2016:

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

As of December 31, 2016

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market funds	$ 8,268	$ 8	$ —	$ 8,276
U.S. Treasury securities	2,523	—	(1)	2,522
U.S. government agency obligations	3,501	1	—	3,502
Corporate bonds	16,683	—	(6)	16,677
Commercial paper	15,206	3	(2)	15,207
Total available-for-sale marketable securities	$ 46,181	$ 12	$ (9)	$ 46,184

All available-for-sale marketable securities are classified in the Company's Balance Sheets as Marketable securities.

The Company classifies its marketable debt securities based on their contractual maturity dates. As of December 31, 2017, the Company's marketable debt securities mature at various dates through July 2018. 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		2016	
Contractual maturity	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Less than one year	$ 43,263	$ 43,230	$ 37,913	$ 37,908

During the years ended December 31, 2017 and 2016, the Company sold shares of its investments in available-for-sale marketable securities with total fair values of $8,755 and $34,003, respectively. The cost of the available-for-sale marketable securities that were sold was determined by specific identification. The sales of the

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investments in available-for-sale marketable securities during each year resulted in realized gains, totaling $5 and $23, 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, 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)

	Less than 12 Months		12 Months or Greater		Total	
As of December 31, 2016	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses
U.S. Treasury securities	$ 2,522	$ (1)	$ —	$ —	$ 2,522	$ (1)
Corporate bonds	9,919	(6)	—	—	9,919	(6)
Commercial paper	5,227	(2)	—	—	5,227	(2)
Total	$ 17,668	$ (9)	$ —	$ —	$ 17,668	$ (9)

As of December 31, 2017, and 2016, the Company held a total of 30 out of 31 positions and 18 out of 34 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, 2017, or 2016. 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.

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

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, 2017, 2016 and 2015.

	Total Accumulated Other Comprehensive Income (Loss)
Balance, December 31, 2014	$ —
Other comprehensive loss before reclassifications	(35)
Amount reclassified from accumulated other comprehensive income	—
Net current period other comprehensive loss	(35)
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)

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

Component of AOCI	Year Ended December 31, 2017	2016	2015	Affected Line Item in the Statements of Comprehensive Loss
Unrealized gains on available-for-sale marketable securities				
Realized gains on sale of securities	$ 5	$ 23	$ —	Other income
	—	—	—	Income tax benefit
	$ 5	$ 23	$ —	

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

5. Prepaid Expenses

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. As of December 31, 2016, the amount of prepaid expenses was $1,530, consisting of $1,256 of prepaid R&D clinical costs, $112 of prepaid insurance, and $162 of other costs.

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

6. Property and Equipment, Net

Property and equipment, net consists of the following:

	December 31,	
	2017	2016
Computer and office equipment	$ 158	$ 149
Laboratory equipment	628	795
Furniture and fixtures	27	173
Leasehold improvements	1,128	8,582
	$ 1,941	$ 9,699
Less accumulated depreciation and amortization	764	8,085
Property and equipment, net	$ 1,177	$ 1,614

Depreciation and amortization expense included in R&D expense and General and administrative expense was $495, $1,465 and $839 for the years ended December 31, 2017, 2016 and 2015, 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 16, *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 stand-by letters of credit as a security deposit under each of the Shelton Lease and the Stamford Lease (refer to Note 16, *Commitments and Contingencies*). The fair value of each letter of credit approximates its contract value. In each case, the Company's bank requires the Company to maintain restricted cash balances to serve as collateral for the letter of credit issued to the respective landlords by the bank. During December 2017, the letter of credit for the Shelton Lease expired and the related restricted cash balance was reclassified to cash and cash equivalents on the Company's Balance Sheet. As of December 31, 2017, 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 remains 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, 2016, the Company had $700 of restricted cash related to the Shelton lease in current assets. As of December 31, 2017 and 2016, the Company had $769 of restricted cash related to the Stamford lease in long-term assets.

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

8. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	December 31,	
	2017	2016
Accounts payable	$ 3,829	$ 4,738
Accrued research projects	2,356	4,352
Accrued professional fees	384	163
Accrued compensation and benefits	1,864	1,514
Accrued other	73	766
	$ 8,506	$ 11,533

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, 2017, there were 32,662,255 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 July 29, 2015, the Company entered into an underwriting agreement, or the Underwriting Agreement, with Stifel, Nicolaus & Company, Incorporated and Piper Jaffray & Co., as representatives of the several underwriters named therein, relating to the issuance and sale by the Company of 3,763,440 shares of its common stock, or the 2015 Offering. The 2015 Offering was made pursuant to the Company's Registration Statement on Form S-3 (File No. 333-203072), filed with the SEC on March 27, 2015 and declared effective on May 13, 2015, and a related prospectus supplement dated July 29, 2015, which was filed with the SEC on July 30, 2015. As part of the 2015 Offering, the Company granted the underwriters an option to purchase 564,516 additional shares of common stock.

On August 4, 2015, the Company closed the 2015 Offering, including the full exercise of the underwriters' option to purchase 564,516 additional shares of common stock, at a public offering price of $18.60 per share. The Company received net proceeds of approximately $75,231, after deducting the underwriting discounts and commissions and offering expenses paid by the Company of $5,269.

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 approximately $86,224, after deducting the underwriting discounts and commissions and offering expenses paid by the Company of $5,891.

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

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, 2017 and 2016 and by level within the fair value hierarchy:

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	$ —

Fair value measurement as of December 31, 2016:

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	$ 12,092	$ 12,092	$ —	$ —
Available-for-sale marketable securities:				
Money market fund	8,276	—	8,276	—
U.S. Treasury securities	2,522	—	2,522	—
U.S. government agency obligations	3,502	—	3,502	—
Corporate bonds	16,677	—	16,677	—
Commercial paper	15,207	—	15,207	—
Restricted cash:				
Commercial money market account	1,469	1,469	—	—
Total financial assets	$ 59,745	$ 13,561	$ 46,184	$ —

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, 2017, 2016 and 2015. There were no transfers of financial assets between Levels 1, 2, or 3 classifications during the years ended December 31, 2017, 2016 and 2015.

11. Collaborations

Chong Kun Dang Pharmaceutical Corporation

In April, 2012, the Company entered into a license agreement with CKDP, or the CKDP Agreement, that provides CKDP with the exclusive rights to develop, manufacture and commercialize products containing CR845/difelikefalin in South Korea. At inception of the CKDP Agreement, the Company received a non-refundable and non-creditable amount of $1,000 and is eligible to receive milestone payments totaling $3,750, relating to pre-defined clinical development ($2,250) and regulatory events ($1,500), as well as royalties on sales of any marketed products containing CR845/difelikefalin. The Company is accounting for the milestones under ASC 605-28 *Revenue Recognition – Milestone Method*. At the time of execution of the CKDP Agreement, there was significant uncertainty as to whether the stated milestones would be achieved. In conjunction with this uncertainty, the Company has determined that the milestones are substantive in nature as they are commensurate with the enhancement of value of the delivered license because they relate to clinical success and advancement within the FDA drug development platform. The milestones also relate solely to past performance and monetary investment of the Company to achieve the clinical advancement.

During the year ended December 31, 2015, the Company met the milestone criteria, as set forth in the CKDP Agreement, for the completion of both a Phase 1b trial of Oral CR845/difelikefalin in the United States and a Phase 2 trial of I.V. CR845/difelikefalin in uremic pruritus patients in the United States. Both milestones were considered to be substantive and, therefore, the total amount of the milestone payments earned, $626 (net of South Korean withholding tax of $124), was recognized as milestone revenue upon achievement of the milestones. The next potential milestone that the Company could be entitled to receive under the CKDP Agreement will be a clinical development milestone for the completion by the Company 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, before South Korean withholding taxes, being due to the Company.

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 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 between 2013 and 2015.

Under the terms of the agreement, the Company received an upfront non-refundable, non-creditable license fee of $15,000. As indicated in Note 2, *Summary of Significant Accounting Policies – Revenue Recognition*, the Company accounts for arrangements of this type under ASC 605-25, *Revenue Recognition - Multiple Element Arrangements.* The Company has identified two deliverables under this guidance: (1) the license; and (2) the R&D services specific to the uremic pruritus field of use. The Company has determined that the license has standalone value because Maruishi has the right to sublicense and manufacture CR845/difelikefalin in Japan. The second deliverable is the R&D services, which also have standalone value as similar services are sold separately by other vendors. Since both license and R&D services separability criteria have been met, they are being accounted for as separate units of accounting from the outset of the arrangement.

As a result, the total value of the arrangement was allocated between the two units of accounting based upon their relative standalone selling prices. The Company used its best estimate of the selling price of these units of accounting, since, as described in Note 2, *Summary of Significant Accounting Policies – Revenue Recognition*, neither VSOE nor TPE was available. To determine these estimates, the Company used a discounted cash flow method that forecasted and analyzed CR845/difelikefalin in the Japanese 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. As a result, at inception of the Maruishi Agreement, the management of the

Company determined that the license and the R&D services deliverables had estimated selling prices of $10,200 and $6,200, respectively.

The resulting percentage allocations were applied to the total consideration. The amount assigned to the license deliverable was recognized immediately as license revenue. The amount assigned to the R&D services unit of accounting was initially recorded as deferred revenue and was recognized as collaborative revenue as the services were provided through July 2015.

Under the terms of the Maruishi Agreement, the Company is also entitled to receive aggregate milestone payments of $8,000 for events performed by Maruishi in Japan and $2,500 for events performed by the Company in the United States. At the time of execution of the Maruishi Agreement, there was significant uncertainty as to whether the stated milestones would be achieved. In conjunction with this uncertainty, the Company has determined that the milestones achieved in the United States are substantive in nature as they are commensurate with the enhancement of value of the delivered license as they relate to clinical success and advancement within the FDA drug development platform. The Company accounts for those milestone payments under ASC 605-28 *Revenue Recognition – Milestone Method*. However, the milestones achieved by Maruishi in Japan are not substantive and are accounted for in accordance with the multiple-element arrangement guidance in ASC 605-25.

During June 2014, Maruishi completed a Phase 1 clinical trial in Japan related to CR845/difelikefalin in acute post-operative pain, which constituted achievement of one of the milestones specified in the Maruishi Agreement and was considered not to be substantive. Accordingly, the Company allocated the non-refundable payment of $480, net of a contractual foreign currency exchange adjustment of $20, to the two deliverables in the same proportion as the initial upfront payment had been allocated. The portion of the payment allocated to the previously delivered license deliverable ($302) was recognized as license revenue entirely at the time of achievement of the milestone. A portion of the payment allocated to the R&D services deliverable ($88) was recognized as collaborative revenue at the time of achievement of the milestone to the extent of R&D services provided through that date and the remainder ($90) was deferred and was recognized as collaborative revenue through July 2015, which was the period during which the Company provided R&D services to Maruishi.

In September 2015, Maruishi initiated a Phase 2 clinical trial of CR845/difelikefalin in Japan for uremic pruritus, which triggered a $1,725 milestone payment (net of contractual foreign currency exchange adjustments of $275) to the Company. At the time of achievement of the milestone, the Company had delivered all deliverables under the Maruishi Agreement. Since the milestone was achieved in Japan, it was deemed not to be substantive. Accordingly, the Company recognized $1,084 as license and milestone revenue and $641 as collaborative revenue in connection with achievement of this milestone.

The next potential milestones that the Company could be entitled to receive under the Maruishi Agreement will be a clinical development milestone for the completion by the Company of the first Phase 3 trial of CR845/difelikefalin in acute pain in the United States and the initiation by Maruishi of a Phase 3 clinical trial of CR845/difelikefalin in Japan for uremic pruritus. If achieved, these milestones will result in payments of $1,000 and $2,000, respectively, before contractual foreign currency exchange adjustments, being due to the Company.

The Maruishi Agreement includes a requirement for the Company to negotiate in good faith with the counterparty, after the execution of the Maruishi Agreement, a separate agreement to supply it with CR845/difelikefalin clinical compound or, at Maruishi's election, CR845/difelikefalin drug substance. However, the Company has no obligation to execute a supply agreement. Furthermore, Maruishi may choose instead to manufacture its own requirements of CR845/difelikefalin drug product and/or drug substance by entering into agreements with contract manufacturing organizations that have the ability to manufacture CR845/difelikefalin. In fact, the parties have never negotiated a master supply agreement.

The Company did not identify the potential supply agreement as a unit of accounting within the overall Maruishi Agreement since the significant terms of the supply agreement had not been negotiated between the parties and no executed agreement exists with designated responsibilities. The Company views this aspect of the Maruishi Agreement as a substantive option subject to negotiation that is separate and independent of the Maruishi Agreement and should not be considered a deliverable. In the event that a supply agreement is negotiated, the price to be paid is 110% of the Company's fully-burdened cost of manufacturing CR845/difelikefalin. The Company concluded that

this price does not represent a significant and incremental discount because it is consistent with the amount that other third parties would charge Maruishi. In the absence of a master supply agreement, the Company and Maruishi entered into separate supply agreements for the Company to supply Maruishi with CR845/difelikefalin. Thus, the only deliverable under these separate supply agreements was the delivery of CR845/difelikefalin clinical compound.

The Company had previously entered into manufacturing and service agreements with third parties to manufacture CR845/difelikefalin. Payments made by the Company to third parties based on firm and fixed commitments by Maruishi to purchase CR845/difelikefalin from the Company are capitalized as prepaid expense. During the manufacturing process, title and risk of loss remains with the third party until the Company paid in full for the material. Once the Company has title to the CR845/difelikefalin and has delivered it to Maruishi, prepaid expense related to that CR845/difelikefalin is reduced with an offset to R&D expense. At that time, Maruishi reimburses the Company for its external and internal costs for purchasing CR845/difelikefalin and processing the sale to Maruishi and the Company recognizes clinical compound revenue for the reimbursement amount. Deposits received from Maruishi prior to delivery of CR845/difelikefalin are recorded as deferred revenue. During the years ended December 31, 2017, 2016 and 2015, the Company recognized clinical compound revenue of $68, $86 and $0, respectively.

The Company is also eligible to receive tiered, low double-digit royalties with respect to any sales of the licensed product sold in Japan by Maruishi. Additionally, the Company can receive sub-license fees (subject to certain credits for milestone payments already made) if Maruishi enters into a sub-license agreement regarding the product candidates.

In March 2017, Maruishi entered into a sub-license agreement with Kissei Pharmaceutical Co. Ltd. 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, during 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 deliverables 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.

The Company incurred R&D expense related to the Maruishi Agreement of $61, $78 (both related to the cost of clinical compound sold to Maruishi) and $1,583 (consisting of clinical trial costs related to the R&D services deliverable) during years ended December 31, 2017, 2016 and 2015, respectively.

12. 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. However, as of January 1, 2015 for officers and January 1, 2016 for employees and non-employee consultants, subsequent grants of Stock Awards vest monthly over a period of four years from the grant date. Stock options initially granted to members of the Company's Board of Directors vest on the date of the Annual Meeting of Stockholders at which their initial term expires based on the class of Director. 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.

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

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, 2018, the aggregate number of shares of common stock that may be issued pursuant to Stock Awards under the 2014 Plan automatically increased from 3,920,613 to 4,900,481. 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

The Company's 2004 Stock Incentive Plan, or the 2004 Plan, as amended, was adopted by the Company's Board of Directors and stockholders. Under the 2004 Plan, the Company has granted stock options to selected officers, employees and consultants of the Company. The Company's Board of Directors administers the 2004 Plan. Options granted under the 2004 Plan have a maximum term of ten years. Options issued generally vest 25% on the first anniversary date of grant and the balance ratably over the next 36 months. Following the effectiveness of the 2014 Plan in January 2014, no additional options or restricted share awards were granted under the 2004 Plan. As of September 30, 2014, the 2004 Plan expired and no further grants of stock options or restricted stock are allowed.

The Company accounts for stock options granted to employees and non-employee members of the Board of Directors in accordance with ASC 718, *Compensation – Stock Compensation*. The Company also occasionally grants stock options to non-employee consultants. 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, 2017 is as follows:

	Number of Options	Weighted-Average Exercise Price	Aggregate Intrinsic Value
Outstanding at December 31, 2016	2,548,408	$ 8.75	
Granted	1,328,500	16.16	
Exercised	(247,892)	6.85	
Forfeited	(136,875)	7.55	
Outstanding at December 31, 2017	3,492,141	$ 11.75	$ 7,739
Weighted average remaining contractual life as of December 31, 2017 (in years)	8.00		
Options exercisable at December 31, 2017	1,556,102	$ 10.25	$ 4,451
Weighted average remaining contractual life as of December 31, 2017 (in years)	6.96		
Options vested and expected to vest as of December 31, 2017	3,492,141	$ 11.75	$ 7,739
Weighted average remaining contractual life as of December 31, 2017 (in years)	8.00		

The total fair value of options vested during the years ended December 31, 2017, 2016 and 2015 was $5,303, $3,589 and $2,489, respectively. The intrinsic value of options exercised during the years ended December 31, 2017, 2016 and 2015 was $2,285, $126 and $1,748, respectively.

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

During the years ended December 31, 2017, 2016 and 2015, the Company granted 1,328,500, 1,078,000 and 774,000 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,		
	2017	2016	2015
Risk-free interest rate	1.85% -2.57%	1.19% - 1.93%	1.43% - 1.89%
Expected volatility	75.3% - 84.5%	67.8% - 77.8%	64.0% - 67.4%
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	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, 2017, 2016 and 2015 was $11.46, $4.28 and $7.17, respectively.

At the end of each fiscal quarter during the years ended December 31, 2017, 2016 and 2015, 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,		
	2017	2016	2015
Risk-free interest rate	1.28% - 2.39%	1.35% - 2.38%	1.81% - 2.15%
Expected volatility	74.6% - 87.3%	70.8% - 75.5%	70.6% - 72.2%
Expected dividend yield	0%	0%	0%
Expected life of non-employee options (in years)	0.62 - 9.94	7.08 - 9.60	8.1 - 8.8

Under ASC 505-50, upon re-measurement of each award, income or expense is recognized during its vesting term.

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, 2017, 2016 and 2015 was $10.16, $4.81 and $10.05, 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.

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

During the years ended December 31, 2017, 2016 and 2015, the Company recognized compensation expense in the accompanying Statements of Comprehensive Loss relating to stock options, as follows:

	Year Ended December 31,		
	2017	2016	2015
Research and development	$ 2,433	$ 1,301	$ 1,073
General and administrative	3,897	1,499	1,441
Total stock option expense	$ 6,330	$ 2,800	$ 2,514

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,		
	2017	2016	2015
Research and development	$ 170	$ (79)	$ 250
General and administrative	200	(20)	100
Total stock option expense	$ 370	$ (99)	$ 350

In connection with the retirement of the Company's former Chief Financial Officer, effective August 15, 2017, or the Modification Date, the Company modified the terms of the former Chief Financial Officer's outstanding Stock Awards to: (1) accelerate 50% of the 98,771 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 for an aggregate of 183,000 shares 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 that would have vested based on their original vesting terms through the term of the consulting services was a Type 1 modification 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 Financial Officer provides continuous service as a consultant.

During the year ended December 31, 2017, with respect to these modifications, the Company recognized $537 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 General and administrative expense in the table above.

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

As of December 31, 2017, 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 $15,913, which is expected to be realized over a weighted average period of 2.96 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, 2017, 2016 and 2015.

13. Income Taxes

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

	December 31,		
	2017	2016	2015
Current:			
Federal	$ —	$ —	$ —
State	(204)	(468)	(397)
	(204)	(468)	(397)
Deferred:			
Federal	—	—	—
State	—	—	—
	—	—	—
Benefit from income taxes	$ (204)	$ (468)	$ (397)

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,		
	2017	2016	2015
Income taxes using U.S. federal statutory rate	34.00%	34.00%	34.00%
State income taxes, net of federal benefit	5.33%	5.44%	5.95%
Tax Cuts and Jobs Act	-44.43%	0.00%	0.00%
Impact of R&D tax credit on effective tax rate	3.25%	3.24%	3.14%
Stock option shortfalls and cancellations	0.21%	-0.07%	-0.03%
Permanent items and other	-0.56%	-0.64%	-0.41%
Change in valuation allowance	2.55%	-41.17%	-41.07%
	0.35%	0.80%	1.58%

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

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

	December 31,	
	2017	2016
Deferred tax assets:		
Net operating loss carryforwards	$ 54,831	$ 57,887
Federal and state tax credits	8,401	6,221
Accelerated depreciation	-	259
Stock-based compensation expense	2,382	1,783
Other	582	641
	66,196	66,791
Deferred tax liabilities:		
Accelerated depreciation	(23)	-
Valuation allowance	(66,173)	(66,791)
Net deferred tax asset	$ —	$ —

A 100% valuation allowance has been recorded on the deferred tax asset as of December 31, 2017 and 2016 because management believes it is more likely than not that the asset will not be realized. The change in the valuation allowance during 2017 and 2016 was $618 and $23,758, respectively.

The Company has a 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. The financial statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. As of December 31, 2017 and 2016, the Company had no unrecognized tax benefits or related interest and penalties accrued. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of interest expense.

At December 31, 2017, the Company had federal and state net operating loss carryforwards of approximately $205,135 and $198,350, respectively. The federal and state tax loss carryforwards will begin to expire in 2026 and 2027, respectively, unless previously utilized. The 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 $7,378 and $1,033, 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 2017 remain open to U.S. federal and state tax examinations.

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%. On December 31, 2017, the Company did not have any foreign subsidiaries and the international aspects of the Act are not applicable.

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

On December 22, 2017, Staff Accounting Bulletin 118, or SAB 118, was issued by the SEC due to the complexities involved in accounting for the Act. SAB 118 requires the Company to include in its financial statements a reasonable estimate of the impact of the Act on earnings to the extent such estimate has been determined. Accordingly, the U.S. provision for income tax for 2017 is based on the reasonable estimate guidance provided by SAB 118. The Company is continuing to assess the impact from the Act and will record adjustments in 2018, if necessary.

14. 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,		
	2017	2016	2015
Basic:			
Weighted average shares outstanding	31,202,842	27,279,008	24,620,372
Diluted:			
Weighted average shares outstanding - Basic	31,202,842	27,279,008	24,620,372
Common stock options *	—	—	—
Denominator for diluted net loss per share	31,202,842	27,279,008	24,620,372

* 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,		
	2017	2016	2015
Net loss	$ (58,125)	$ (57,280)	$ (24,690)
Weighted-average common shares outstanding:			
Basic and Diluted	31,202,842	27,279,008	24,620,372
Net loss per share:			
Basic and Diluted	$ (1.86)	$ (2.10)	$ (1.00)

As of December 31, 2017 and 2016, 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.

15. 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. Effective January 1, 2015, 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, 2017, 2016 and 2015, employer contributions to the plan were $174, $118 and $80, respectively.

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

16. Commitments and Contingencies

Contractual obligations and commitments as of December 31, 2017, comprising future minimum lease payments under the Company's Stamford lease, were as follows:

	Payment Due for the Year Ending December 31,						
	2018	2019	2020	2021	2022	Thereafter	Total
Stamford operating lease	$ 1,091	$ 1,215	$ 1,240	$ 1,264	$ 1,288	$ 1,164	$ 7,262

Stamford Operating Lease

In December 2015, the Company entered into a lease agreement, or the Stamford Lease, with Four Stamford Plaza Owner LLC, or the Landlord, 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, 2017 and 2016, the balance of deferred lease obligation, representing the difference between cash rent paid and straight-line rent expense, was $876 and $583, respectively. The Stamford Lease is renewable for one five-year term.

As of the Commencement Date, the Stamford landlord had made tenant improvements of approximately $1,094 to the leased premises. Such amount was included in Property and equipment, net and in Deferred lease obligation on the Company's Balance Sheet on that date. 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, 2017 and 2016, the balance of Deferred lease obligation related to tenant improvements was $842 and $987, respectively.

Total rent expense under the Stamford Lease was $935 and $797 for the years ended December 31, 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.

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 and $665 for the years ended December 31, 2016 and 2015, respectively.

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

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. As of December 31, 2016, the balance of the letter of credit was $700, which was secured with restricted cash (refer to Note 7, *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 and $67 for the year ended December 31, 2015.

17. Legal Matters

From time to time, the Company may become involved in arbitrations or legal proceedings that arise in the ordinary course of its business. The Company cannot predict the timing or outcome of these claims and proceedings. Currently, the Company is not involved in any such arbitration and/or legal proceeding that it expects to have a material effect on its financial condition, results of operations or business.

18. Quarterly Results of Operations (Unaudited)

The following tables contain selected financial data for each quarter of the years ended December 31, 2017 and 2016. 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, 2017 and 2016. The operating results for any period are not necessarily indicative of results for any future periods.

	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*).

	Year Ended December 31, 2016			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$ 7	$ 79	$ —	$ —
Net loss - Basic and Diluted	(10,692)	(13,075)	(11,542)	(21,971)
Loss per share - Basic and Diluted	$ (0.39)	$ (0.48)	$ (0.42)	$ (0.81)

EXHIBIT 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-216657) of Cara Therapeutics Inc.
(2) Registration Statement (Form S-3 No. 333-203072) of Cara Therapeutics Inc.
(3) Registration Statement (Form S-8 No. 333-216606) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.
(4) Registration Statement (Form S-8 No. 333-210096) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc.
(5) Registration Statement (Form S-8 No. 333-203057) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc., and
(6) Registration Statement (Form S-8 No. 333-193905) pertaining to the 2004 Stock Incentive Plan, as amended, and 2014 Equity Incentive Plan;

of our report dated March 15, 2018, with respect to the financial statements of Cara Therapeutics Inc., included in this Annual Report (Form 10-K) of Cara Therapeutics Inc., for the year ended December 31, 2017.

/s/ Ernst & Young LLP

Stamford, Connecticut
March 15, 2018

EXHIBIT 31.1

Certification of Chief Executive Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Derek Chalmers, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cara Therapeutics, Inc.;

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

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

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

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 15, 2018

By: /s/ Derek Chalmers
DEREK CHALMERS, Ph.D., D.Sc.
CHIEF EXECUTIVE OFFICER

EXHIBIT 31.2

Certification of Chief Financial Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Mani Mohindru, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cara Therapeutics, Inc.;

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

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

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

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 15, 2018

By: /s/ Mani Mohindru
MANI MOHINDRU, Ph.D.
CHIEF FINANCIAL OFFICER

EXHIBIT 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

In connection with the Annual Report on Form 10-K of Cara Therapeutics, Inc. (the "Company") for the year ended December 31, 2017, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Derek Chalmers, Ph.D., D.Sc., as Chief Executive Officer of the Company, and Mani Mohindru, Ph.D., as Chief Financial Officer of the Company, each hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of his knowledge, based upon a review of the Report:

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

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

/s/ DEREK CHALMERS
Name: Derek Chalmers, Ph.D., D.Sc.
Title: Chief Executive Officer
Date: March 15, 2018

/s/ MANI MOHINDRU
Name: Mani Mohindru, Ph.D.
Title: Chief Financial Officer
Date: March 15, 2018