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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, 2015
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.)**

1 Parrott Drive
Shelton, Connecticut 06484
(Address of principal executive offices)

Registrant's telephone number, including area code: (203) 567-1500

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 or a smaller reporting company. See definition of "large accelerated filer", "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller Reporting Company	☐

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 $208,552,053. For purposes of this calculation, shares of common stock held by directors and officers and their affiliated entities at June 30, 2015 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 3, 2016 was 27,254,863.

DOCUMENTS INCORPORATED BY REFERENCE

Specified portions of the registrant's Definitive Proxy Statement with respect to its 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this report. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

CARA THERAPEUTICS, INC.
2015 ANNUAL REPORT ON FORM 10-K

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PART I

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

Cautionary Note Regarding Forward-Looking Statements

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

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

- the success and timing of our clinical trials, including our clinical trial programs for I.V. CR845 in acute pain and uremic pruritus and Oral CR845 in acute and chronic pain, and the reporting of clinical trial results;
- the potential removal of the investigational new drug application, or IND, clinical hold relating to our pending adaptive pivotal trial for I.V. CR845 in postoperative pain, and the resumption of the trial;
- the potential regulatory development pathway for I.V. CR845 in uremic pruritus, including the potential request for breakthrough therapy and orphan drug status;
- our plans to develop and commercialize I.V. CR845 and our other product candidates, including Oral CR845;
- 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 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 I.V. and Oral CR845, and the labeling under any approval we may obtain;
- the anticipated commercial launch of our lead product candidate, I.V. CR845;
- the potential of future scheduling of I.V. CR845 by the United States Drug Enforcement Administration ("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 CKD, 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, including the net proceeds from our recently completed follow-on offering, 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 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 and 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 pain and pruritus by selectively targeting kappa opioid receptors. We are developing a novel and proprietary class of product candidates that target the body's peripheral nervous system.

We commenced operations in 2004, and our primary activities to date have been organizing and staffing our company, developing our 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.

According to IMS Health, an independent market research firm, the total U.S. market for pain management pharmaceuticals was $37.2 billion in 2015. The prescription pain management market in the United States is dominated by opioid analgesics, which, according to IMS Health data, represented 57% of the 433 million analgesic prescriptions written in 2015 and accounted for sales of $9.1 billion in that year. Opioid analgesics decrease the perception of pain by stimulating mu, delta and/or kappa opioid receptors. All of these receptors are involved in modulating pain signals. The most widely used opioid analgesics, including hydrocodone, oxycodone, morphine, and fentanyl, act primarily through the activation of mu opioid receptors in the 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.

Our most advanced product candidate is based on our new chemical entity, CR845, which is designed to produce pain relief by specifically stimulating kappa, rather than mu, opioid receptors. We have designed CR845 with specific chemical characteristics to restrict its entry into the CNS and further limit CR845's mechanism of action to kappa opioid receptors in the peripheral nervous system, which consists of the nerves outside 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 side effects, including acute psychiatric disorders. Since CR845 is designed to modulate pain signals without activation of mu or kappa opioid receptors in the CNS, it is not expected to produce the psychiatric side effects of centrally-active prior kappa opioids or the CNS related side effects of mu opioids. CR845 has been administered to over 700 human subjects in Phase 1 and Phase 2/3 clinical trials as an intravenous infusion, rapid intravenous injection or oral capsule or tablet and was considered to be safe and well tolerated in these clinical trials.

Based on the clinical trials and preclinical studies we have completed to date, we believe that product candidates based on CR845, if approved, will be attractive to both patients and physicians as a treatment for moderate-to-severe pain due to the following attributes:

- novel, peripherally-acting, kappa opioid receptor mechanism of action;
- strong evidence of efficacy and anti-inflammatory activity;
- 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 does not interact with the liver enzymes responsible for the metabolism of most commonly used classes of drugs; and
- availability in intravenous, or I.V., form for acute pain treatment in the hospital setting and oral form for treatment of acute and chronic pain in either a hospital or outpatient setting.

Our most advanced product candidate I.V. CR845, has demonstrated significant pain relief and a favorable safety and tolerability profile in three randomized, double-blind, placebo-controlled Phase 2 clinical trials, in patients with acute postoperative pain who were undergoing soft tissue (laparoscopic hysterectomy) and hard tissue (bunionectomy) surgery, without inducing many of the undesirable side effects typically associated with currently available pain therapeutics.

In addition, in the fourth quarter of 2014, we successfully completed a Human Abuse Liability, or HAL, trial of I.V. CR845. The top-line results from this HAL trial indicate that I.V. CR845 met the trial's primary endpoint by demonstrating highly statistically significant lower "drug liking" scores as measured by visual analog scale (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, I.V. CR845 showed no "drug liking" dose response as both doses of I.V. CR845 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 to be the first non-scheduled or low (Schedule V) scheduled peripheral opioid for acute pain.

In April 2015, we completed an End-of-Phase 2 meeting with the FDA, to discuss the design of pivotal trials for our I.V. CR845 product candidate in acute pain. In September 2015, we initiated the Phase 3 program for our I.V. formulation of CR845 in postoperative pain with the dosing of the first subjects in an adaptive pivotal trial in patients undergoing a range of abdominal surgeries (see *Our Product Candidates – I.V. CR845*, below, for details of the Phase 3 trial).

In February 2016, the FDA advised us that our adaptive pivotal trial of I.V. CR845 for postoperative pain had been placed 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 that was included in the clinical trial protocol. Four patients out of 90 total patients dosed to date, all of whom were in the highest I.V. CR845 dose group (5 ug/kg), exhibited transient serum sodium levels equal to or greater than 150 mmol/L (mild-to-moderate hypernatremia). All four patients were asymptomatic and sodium levels resolved to normal levels (less than 146 mmol/L) within 24 hours post-dosing with standard fluid management. No patients in the other two dose groups (2 ug/kg and 1 ug/kg) exhibited serum sodium levels greater than 150 mmol/L. A review of unblinded safety data has been undertaken by both us and the Independent Data Monitoring Committee in accordance with the clinical trial protocol.

The most common adverse events (> 5%) reported across treatment groups and placebo so far were nausea, hypernatremia, abdominal distension and procedural hypotension. All cases of abdominal distension and procedural hypotension were attributed to the surgical procedure and not to the dosing of I.V. CR845. There were no cases of respiratory depression, no adverse events greater than Grade 1, and no CR845-associated serious adverse events have been reported. We anticipate continuing the trial following FDA review of the patient safety data and removal of the clinical hold.

Based on previous guidance from the FDA, we believe we will require 1,500 total exposures to I.V. CR845, including all Phase 1, Phase 2 and Phase 3 trials, prior to submitting a new drug application, or NDA. We believe our planned clinical trials and our clinical trials completed to date will result in a sufficient number of drug exposures to support an NDA.

We are also developing an oral version of CR845, or Oral CR845, 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.

In August 2015, we advanced our tablet formulation of Oral CR845 into a Phase 2a clinical trial in patients with osteoarthritis, or OA, of the knee or hip. In December 2015, we announced positive top-line results from this Phase 2a trial. The results showed a dose-related reduction in mean baseline pain score up to 34% after two weeks, with a statistically significant reduction in mean rescue medication for the top 5.0 mg dose group of approximately 80%. See the section titled “Our Product Candidates – Oral CR845”, below, for details of this Phase 2a OA trial. We plan to initiate a double-blind, multiple dose Phase 2b clinical trial of Oral CR845 in the second half of 2016. The Phase 2b trial will include twice-daily doses of three tablet strengths of Oral CR845 or placebo over an eight-week treatment period in patients with moderate-to-severe pain associated with OA.

CR845 has exhibited anti-pruritic, or anti-itch, potency in standard preclinical models. In the fourth quarter of 2014, we reported positive top-line dose-ranging pharmacokinetic, or PK, and safety data from a Phase 1b clinical trial, which was part A of a Phase 2 proof-of-concept trial of I.V. CR845 for the treatment of uremic pruritus, a systemic condition with high prevalence in dialysis patients, for which there are no approved therapeutics in the United States. In July 2015, we reported positive top-line efficacy results from Part B of this Phase 2 proof-of-concept trial, in which we observed that I.V. CR845 demonstrated statistically significant results on the primary endpoint of reducing worst itch intensity as well as the secondary endpoint of quality of life improvements**.** We also observed I.V. CR845 to have a favorable safety and tolerability profile in the trial.

Based on the results of this trial, during the fourth quarter of 2015 we completed a guidance meeting with the FDA, the outcome of which will guide the overall design of our Phase 3 clinical trial program for I.V. CR845 for the treatment of uremic pruritus. Subject to the feedback from the FDA, we intend to initiate a first Phase 2/3 adaptive pivotal trial in uremic pruritus in the first half of 2016.

In the future, we intend to request breakthrough therapy designation and orphan drug status for I.V. CR845 for the treatment of uremic pruritus. If granted by the FDA, breakthrough designation could provide for expedited regulatory review of I.V. CR845 for the treatment of uremic pruritus, and orphan drug status could confer marketing exclusivity benefits.

We are also developing a peripherally-acting cannabinioid receptor agonist, CR701, which has demonstrated potent activity in preclinical models of inflammatory and neuropathic pain without producing CNS-related side effects. In addition, CR701 exhibits substantial oral bioavailability in preclinical studies. We have successfully conducted 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 to initiate a Phase 1 ascending single-dose tolerance and PK study in healthy human subjects.

CR845 and CR701 were discovered by our scientists. We own eight U.S. patents and two allowed applications with claims covering compositions of matter and methods of use for CR845. The earliest U.S. patent claiming CR845 compositions will expire no earlier than November 12, 2027. We also own four issued U.S. patents that cover the compound CR701, CR701 as a member of a class of related compounds and methods of using these compounds. These U.S. patents are due to expire no earlier than June 20, 2028.

We anticipate developing a distribution capability and commercial organization in the United States to market and sell our I.V. product candidates in the acute care setting, while out-licensing commercialization rights in certain geographical territories outside of the United States. For Oral CR845, we plan to explore late-stage development and commercialization partnerships both in the United States and worldwide. We have entered into collaboration agreements for both I.V. and Oral CR845 with Maruishi Pharmaceuticals, or Maruishi, in Japan and Chong Kun Dang Pharmaceutical Corp., or CKD, in South Korea, which provide them the exclusive right to develop and market CR845 for certain indications within those territories. As of December 31, 2015, we had received approximately $28 million in payments in connection with these collaborations and were eligible to receive further payments and royalties upon the achievement of future development and commercialization milestones.

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

Product Candidate	Primary Indication(s)	Status	Commercialization Rights
I.V. CR845	Acute Pain	Phase 3 Clinical Trial Program Initiated (currently on IND clinical hold)	Cara (worldwide, other than Japan and South Korea) Maruishi (Japan) CKD (South Korea)
I.V. CR845	Uremic Pruritus	FDA Guidance Meeting Complete	Cara (worldwide, other than Japan and South Korea) Maruishi (Japan) CKD (South Korea)
Oral CR845	Acute & Chronic Pain	Phase 2a OA Clinical Trial Top-Line Data Reported	Cara (worldwide, other than Japan and South Korea) Maruishi (Japan–for acute pain indication only) CKD (South Korea)
CR701	Neuropathic & Inflammatory Pain	Preclinical	Cara (worldwide)

The Market Opportunity – Pain Management

Pain is generally categorized by its duration as either acute or chronic, by its severity, as 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. According to IMS Health, the total U.S. market for pain management pharmaceuticals was $37.2 billion in 2015. In 2012, according to Visiongain, an independent industry research company, total sales for pain therapies worldwide, exceeded $63 billion.

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 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 a poor side effect and abuse liability profile, 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 IMS Health, opioid analgesics represented approximately 57% of the nearly 433 million analgesic prescriptions written in 2015, accounting for $9.1 billion in sales.

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 U.S. 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), 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 NSP Audit.

According to recently updated 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 "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, or OBD, which contributes to the severity of postoperative ileus, or POI. 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 United States Drug Enforcement Agency, or 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, 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.

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. The sensation of pruritus is transmitted through slow-conducting unmyelinated C-polymodal and possibly type A delta nociceptive neurons with free nerve endings located near the dermoepidermal junction or in the epidermis. These neurons appear to be located more superficially and are more sensitive to pruritogenic substances than pain receptors. Activators of these nerves include histamine, neuropeptide substance P, serotonin, bradykinin, proteases (e.g., mast cell tryptase), and endothelin (which stimulates the release of nitric oxide). Impulses are transmitted from the dorsal root ganglion to the spinothalamic tract. Additionally, opioids are known to modulate the sensation of pruritus, both peripherally and centrally. Stimulation of mu opioid receptors accentuates pruritus, while stimulation of kappa receptors suppress pruritus.

Pruritus may be classified into the following categories on the basis of the underlying causative disease: renal or uremic pruritus, cholestatic pruritus, hematologic pruritus, endocrine pruritus, pruritus related to malignancy, dermatological pruritus and idiopathic generalized pruritus. According to a study Cara conducted with IMS Health 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.

Uremic Pruritus

Renal or uremic pruritus can occur in patients with chronic renal failure (CRF) and is most often seen in patients receiving hemodialysis (HD). According to Fresenius Medical Care, a world leading provider of products and medical care for dialysis patients, there were over 400,000 patients in the United States and 2.2 million globally undergoing HD in 2013. It is estimated that 40-50% of these patients suffer from renal or uremic pruritus according to a study of dialysis patients ("Pruritus in haemodialysis patients: international results from the Dialysis Observation and Practice Patterns Study (DOPPS)", Pisoni et al. 2006).

Currently, there are no approved products in the United States to treat renal or uremic pruritus. 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, approved to treat uremic pruritus 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 to refuse 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 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.

Our Product Candidates

I.V. CR845 – Acute Pain

Our most advanced product candidate, I.V. CR845, is an injectable version of our first-in-class, peripheral kappa opioid receptor agonist, which is intended for the treatment of acute pain in an acute care setting. I.V. CR845 is designed to provide pain relief without stimulating mu opioid receptors and therefore without mu opioid-related side effects, such as nausea, vomiting, respiratory depression and euphoria.

I.V. CR845 has been well tolerated and demonstrated consistent efficacy in three randomized, double-blind, placebo-controlled Phase 2 clinical trials. Two of these trials were in patients undergoing a laparoscopic hysterectomy, a soft tissue surgical procedure, and a third trial was in patients undergoing a bunionectomy, a hard tissue surgical procedure. I.V. CR845 administration resulted in statistically significant reductions in pain intensity, as measured by the sum of pain intensity difference, or SPID, the FDA-recommended endpoint. In addition, in both surgical models, I.V. CR845 exhibited an ability to decrease the opioid-related adverse events, or AEs, of nausea and vomiting associated with current therapies with no evidence of drug-related respiratory depression. According to research conducted at Duke University, post-operative AEs associated with currently approved opioids, such as nausea and vomiting, 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 I.V. CR845 has the potential to significantly reduce the length of hospital stays, thereby reducing overall healthcare costs.

The safety profile of I.V. CR845 has been documented in nine clinical trials, including six Phase 1 and three Phase 2 studies. In these trials, CR845 was administered to approximately 500 human subjects at single or repeat doses ranging from 1mcg/kg to 40 mcg/kg up to a 1 week period, in the form of I.V. infusion or I.V. bolus injection. I.V. CR845 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 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 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.

In September 2015, we initiated our Phase 3 clinical trial program for I.V. CR845 in postoperative pain with the dosing of the first subjects in an adaptive pivotal 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 I.V. CR845 or placebo administered both prior to and following abdominal surgery in male and female patients. The trial will enroll up to 600 patients undergoing either hysterectomy, prostatectomy, hemi-colectomy or ventral hernia, all of which are associated with moderate-to-severe postoperative pain, at approximately 30 clinical sites within the United States. Three dose levels of I.V. CR845 (1.0, 2.0 and 5.0 ug/kg

I.V.) will be compared to placebo, with an interim conditional power assessment to identify optimal doses that will be used to complete the enrollment of this study. The primary efficacy measure is the Change in Pain Intensity over the 24-hour postoperative period (AUC-24) using the patient-reported Numeric Rating Scale (NRS) score collected at pre-specified time points through 24 hours. Postoperative nausea and vomiting (PONV) will be evaluated as a secondary efficacy measure. The impact of I.V. CR845 treatment on inflammatory biomarkers will also be explored.

In February 2016, the FDA advised us that our adaptive pivotal trial of I.V. CR845 for postoperative pain had been placed 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 that was included in the clinical trial protocol. Four patients out of 90 total patients dosed to date, all of whom were in the highest I.V. CR845 dose group (5 ug/kg), exhibited transient serum sodium levels equal to or greater than 150 mmol/L (mild-to-moderate hypernatremia). All four patients were asymptomatic and sodium levels resolved to normal levels (less than 146 mmol/L) within 24 hours post-dosing with standard fluid management. No patients in the other two dose groups (2 ug/kg and 1 ug/kg) exhibited serum sodium levels greater than 150 mmol/L. A review of unblinded safety data has been undertaken by both us and the Independent Data Monitoring Committee in accordance with the clinical trial protocol.

The most common adverse events (> 5%) reported across treatment groups and placebo so far were nausea, hypernatremia, abdominal distension and procedural hypotension. All cases of abdominal distension and procedural hypotension were attributed to the surgical procedure and not to the dosing of I.V. CR845. There were no cases of respiratory depression, no adverse events greater than Grade 1, and no CR845-associated serious adverse events have been reported. We anticipate continuing the trial following FDA review of the patient safety data and removal of the clinical hold.

I.V. CR845 – Uremic Pruritus

Phase 1b Safety and PK in Dialysis Patients (CLIN2005) –Part A

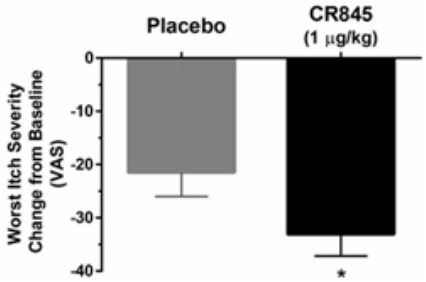
In 2014, we conducted a Phase 1b clinical trial, which was part A of a Phase 2 proof-of-concept trial, as a double-blind, randomized, placebo-controlled trial designed to evaluate the safety and PK of I.V. CR845 in 24 hemodialysis patients. I.V. CR845 was administered in the form of I.V. bolus injection at doses ranging from 0.5 mcg/kg to 2.5mcg/kg after each dialysis session up to three times per week. Pharmacokinetic analysis indicated that I.V. CR845 exhibited dose linear increases in maximum serum concentration (“Cmax”) and total CR845 exposure, using a common measurement method known as area under the curve, or AUC, with an approximate 10-fold increase in AUC across doses in these dialysis patients compared to normal subjects.

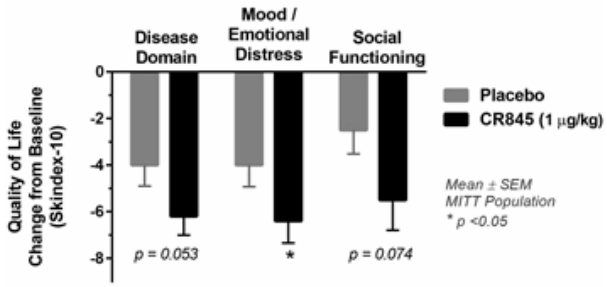
I.V. CR845 was observed to be safe and well tolerated over the one-week dosing period. The most common AEs were transient facial tingling and headache. No serious AEs were reported. Although uremic pruritus was not an inclusion criterion for randomization, three subjects entered the trial with “worst itching” baseline scores in the moderate-to-severe range, > 4.0 on a 10.0 point visual analog scale, or VAS. All three of these subjects received dosing of I.V. CR845 up to three times per week (with two subjects receiving 1 mcg/kg and one receiving 2.5mcg/kg) and ended the one-week dosing period with reported “worst itching” scores of 1.0 or less on a VAS.

Phase 2 Efficacy in Dialysis Patients (CLIN2005) – Part B

Part B was a randomized, double-blind, placebo-controlled Phase 2 proof-of-concept trial, which measured the efficacy of I.V. CR845 compared to placebo in reducing the intensity of itch in dialysis patients with uremic pruritus who had baseline “worst itching” scores of 4.0 or greater on a VAS over a two-week dosing period. 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 previously validated self-assessment scales. The study enrolled a total of 65 dialysis patients at 21 sites in the United States. During the third quarter of 2015, we reported top-line efficacy results from Part B of the Phase 2 proof-of-concept trial.in which we observed that I.V. CR845 demonstrated statistically significant results on the primary endpoint of reducing worst itch intensity as well as the secondary endpoint of quality of life improvements (Figure 1)**.** We also observed I.V. CR845 to have a favorable safety and tolerability profile in the trial.

Figure 1: CR845 Significantly Reduces Itch Severity and Improves Quality of Life in Hemodialysis Patients with Uremic Pruritus





Oral CR845

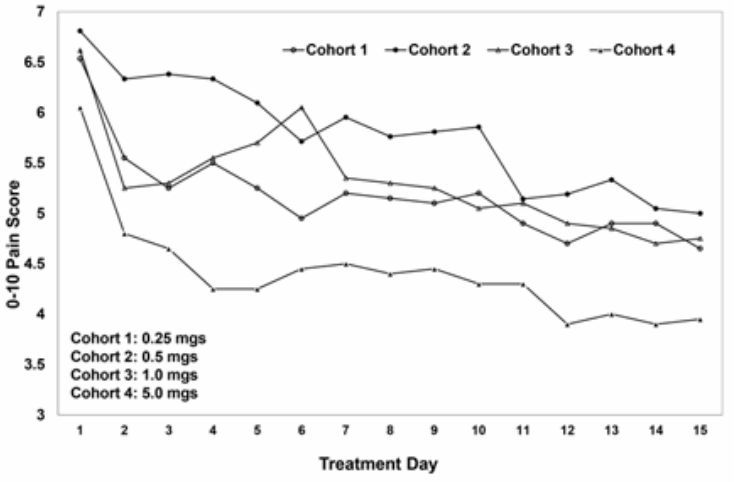
We are also developing an oral version of CR845. We believe Oral CR845 will address a significant unmet medical need for a safer alternative to opioids, NSAIDs or CNS anticonvulsant agents for the treatment of moderate-to-severe acute and chronic pain. In addition to the efficacy benefits that CR845 has previously demonstrated, we believe a significant benefit of Oral CR845 in the acute and chronic pain market would 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 2a Trial of Oral CR845 (CLIN 2001-PO)

In August 2015, we advanced a tablet formulation of Oral CR845 into a Phase 2a clinical trial in patients with 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 tablets dosed over a two-week treatment period in OA patients experiencing moderate-to-severe pain, defined as >4 on an 11-point Numerical Rating Scale, or NRS, at baseline. 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 enrolled at five sites in the U.S. (Figure 1). In addition to safety and PK observations, CR845's effectiveness was assessed by: change from baseline in joint pain using the NRS, which was measured daily, change from baseline in the Western Ontario and McMaster Osteoarthritis Index, or WOMAC, which was measured at the end of Weeks 1 and 2 of treatment, change from baseline in rescue medication use, measured daily, and Patient Global Assessment, or PGA, which was measured on the last day of the study. Acetaminophen was the only allowable rescue medication. PK analyses indicated dose-proportional exposure of CR845 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 show a dose-related reduction in mean baseline pain score up to 34% after two weeks, with a statistically significant reduction in mean rescue medication for top 5.0 mg dose of approximately 80% (ANOVA: p= 0.02, for 5.0 mg vs lower dose groups) (Figure 2). 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 (Cochran-Mantel-Haenszel test, p=0.02, 2-sided). In this trial, all four tablet strengths were observed to be safe and well tolerated. The Phase 2a trial establishes therapeutic doses and a dosing regimen for a larger double-blind, placebo-controlled Phase 2b trial, which we plan to conduct during the second half of 2016.

Figure 2: Arithmetic Average Numeric Pain Rating Scores by Randomized Treatment Assignment (Cohort) and Treatment Day (Imputed Results Using the Last Observation Carried Forward [LOCF])



CR701

In addition to our CR845 family of peripheral kappa agonists, we have discovered and are developing 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.

Our Strategy

Our strategy is to develop and commercialize a novel and first-in-class portfolio of peripherally-acting analgesics, focused initially on kappa opioid receptor agonists, with I.V. CR845 and Oral CR845 as the lead candidates, and subsequently on cannabinoid receptor agonists. We have designed and are developing product candidates which have clearly defined clinical development programs and target large commercial market opportunities. The key elements of our strategy are as follows:

Continue to advance I.V. CR845 to approval for treating moderate-to-severe acute pain in acute care settings in the United States. In April 2015, we completed an End-of-Phase 2 meeting with the FDA, to discuss the design of our pivotal trials for our I.V. CR845 product candidate in acute pain. In September 2015, we initiated our Phase 3 clinical trial program for I.V. CR845 in postoperative pain with the dosing of the first subjects in an adaptive pivotal trial in patients undergoing a range of abdominal surgeries. In February 2016, the FDA placed this trial on IND clinical hold pending a safety review. The clinical hold was based on a stopping rule related to elevated serum sodium levels greater than 150 mmol/L that was included in the clinical trial protocol. A review of unblinded

safety data has been undertaken by both us and the Independent Data Monitoring Committee in accordance with the clinical trial protocol. We anticipate continuing the trial pending FDA review of the patient safety data. Based on previous guidance from the FDA, we believe we will require 1,500 total exposures to I.V. CR845, including all Phase 1, Phase 2 and Phase 3 trials, prior to submitting a new drug application, or NDA. We believe our planned clinical trials and our clinical trials completed to date will result in a sufficient number of drug exposures to support an NDA.

Build a sales and marketing organization to commercialize I.V. CR845 for acute pain in the acute care setting in the United States. We are planning to establish a hospital-based sales force to market I.V. CR845 to physicians in the United States. We believe that a sales force of approximately 80 sales professionals can 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 development and commercialization of I.V. CR845 outside of the United States. We do not intend to build a sales and marketing infrastructure outside the United States. We will seek partnerships and collaborations with companies that have development and commercialization expertise for the commercialization of I.V. CR845 in countries or regions outside of the United States. We have already signed development and commercialization agreements with Maruishi for I.V. CR845 and acute indications of Oral CR845 in the Japanese market and Chong Kun Dang for I.V. and Oral CR845 in the South Korean market.

Advance Oral CR845 through a Phase 2b clinical trial and seek a global development and commercialization partner. The market for oral chronic pain medications is large and requires a significant sales and marketing infrastructure that other global pharmaceutical partners are better positioned to provide than we are. In December 2015, we announced positive top-line results from our Phase 2a clinical trial of Oral CR845 in patients with OA of the knee or hip. We plan to initiate a double-blind, multiple dose Phase 2b clinical trial of Oral CR845 in the second half of 2016. The Phase 2b trial will include twice-daily doses of three tablet strengths of Oral CR845 or placebo over an eight-week treatment period in patients with moderate-to-severe pain associated with OA. Following our Phase 2b trial, we intend to seek a global or regional partner for continued development and future commercialization of Oral CR845 internationally. We would intend to retain rights to co-promote Oral CR845 in the U.S.

Establish proof-of-concept for the utility of CR845 in additional, non-analgesic, clinical indications, such as pruritus, and seek additional global development and commercialization partners. Based on potent anti-pruritic (anti-itch) properties we observed CR845 to possess in standard preclinical models of itch, we began exploring I.V. CR845 as a potential treatment of uremic pruritus, a condition that is prevalent among kidney dialysis patients and is resistant to both anti-histamine and steroid treatments and for which there are no approved therapeutics in the United States. In the fourth quarter of 2014, we reported positive top-line dose-ranging PK and safety data from a Phase 2 proof-of-concept trial of I.V. CR845 for the treatment of uremic pruritus. In July 2015, we reported positive top-line efficacy results from this trial, in which we observed that I.V. CR845 demonstrated statistically significant results on the primary endpoint of reducing worst itch intensity as well as the secondary endpoint of quality of life improvements. We also observed I.V. CR845 to have a favorable safety and tolerability profile in the trial. Based on the results of this trial, during the fourth quarter of 2015 we completed a guidance meeting with the FDA, the outcome of which will guide the overall design of our Phase 3 clinical trial program for I.V. CR845 for the treatment of uremic pruritus. Subject to the feedback from the FDA, we intend to initiate a first Phase 2/3 adaptive pivotal trial in uremic pruritus in the first half of 2016.

Commercial Partnerships

Maruishi Pharmaceutical Co., Ltd.

In April 2013, we entered into a license agreement with Maruishi ("Maruishi") (the "Maruishi Agreement") under which we granted Maruishi an exclusive license to develop, manufacture and commercialize drug products containing CR845 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 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 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 in Japan. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845 in the United States. We also agreed to use commercially reasonable efforts to supply Maruishi with its requirements of drug product containing CR845 or, at Maruishi's election, CR845 drug substance. Maruishi may choose instead to manufacture its own requirements of CR845 drug product and/or drug substance.

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 in acute post-operative pain. In September 2015, Maruishi initiated a Phase 2 clinical trial of CR845 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, which was received in October 2015. We are also eligible to receive a one-time sales milestone of one billion Yen (approximately $8.8 million based on the US Dollar/Yen exchange rate as of March 3, 2016) 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 CKD (the "CKD Agreement") under which we granted CKD an exclusive license to develop, manufacture and commercialize drug products containing CR845 in South Korea. CKD is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845 in South Korea. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845 in the United States. We also agreed to supply CKD with its requirements of CR845 drug substance.

Under the terms of the CKD 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 CKD Agreement, CKD 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 CKD 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. CKD'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 CKD upon the achievement of clinical development milestones under the CKD Agreement. During 2015, we received a total of $0.6 million, net of foreign taxes, from CKD upon the achievement of two clinical development milestones under the CKD Agreement. The CKD Agreement continues until CKD no longer has any obligation to pay us royalties on any product. Either we or CKD may terminate the CKD Agreement for the other party's breach of the CKD Agreement or bankruptcy. CKD may terminate the CKD 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 CKD, or a third party commercializes a product containing a compound identical to CR845 without infringing any of the licensed patent rights in South Korea. We may terminate the CKD Agreement if CKD challenges the licensed patent rights or if a third party in South Korea owns an issued patent that claims CR845 and CKD'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 I.V. CR845 in the United States. We anticipate developing a distribution capability and commercial organization in the United States to market and sell our I.V. product candidates in the acute care setting, while out-licensing commercialization rights in certain geographical territories outside of the United States. For Oral CR845, we plan to explore late-stage development and commercialization partnerships both in the United States and worldwide.

We have commissioned market research for I.V. CR845 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 demonstrated statistically significant pain relief and statistically significant reductions in nausea and vomiting. As a result, we believe I.V. CR845 is well positioned to address unmet needs in the postoperative pain market.

Additionally in September 2014, we conducted a quantitative primary market research study to evaluate the commercial opportunity of Oral CR845 for both acute and chronic pain in the United States. The study surveyed 100 physicians (Pain Specialists, Orthopedic Surgeons, Primary Care Physicians and Rheumologists) on their current treatment of acute and chronic pain. Physicians were then shown a profile of oral CR845 based on Cara's Phase 2 safety and efficacy data in laparoscopic hysterectomy and bunionectomy pain. Additionally, physicians were shown different levels of DEA drug scheduling for CR845 to evaluate. Key results were:

- 84% of surveyed physicians report they are likely to prescribe the product to their patients with moderate-to-severe pain, with 55% "very to extremely likely."
- Physicians rated CR845 very favorably on features that were important when making treatment decisions such as safety profile and low abuse potential.
- Other key benefits mentioned included the fact that it has an appealing mechanism of action, and has lower CNS side effects.
- Oral CR845 received significant preference share (>30%) for patients with acute and chronic moderate-to-severe pain.

As a result, we believe that oral CR845 represents a significant opportunity for patients in both acute and chronic pain.

Finally in 2015, we commissioned a qualitative market research study of nephrologists to evaluate the commercial potential of I.V. CR845 for uremic pruritus. The study suggests CR845 would be well received by nephrologists, if approved. The key findings from the study were:

- There is a clear unmet need to manage uremic pruritus among dialysis patients.
- Currently, there are no effective options for severe uremic pruritus.
- CR845 demonstrates impressive efficacy for uremic pruritus.
- Physicians were impressed with placebo-like adverse event profile.
- I.V. CR845 can easily be incorporated into dialysis sessions.

As a result, we believe that I.V. CR845 is well positioned to address the unmet needs for hemodialysis patients suffering from uremic pruritus.

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. Eight issued U.S. patents directed to CR845 and its uses, and two allowed applications, when issued, 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.

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 compositions of matter covering the compounds, 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. Consequently, we do not know whether any of our product candidates will be 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 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 (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

Our synthetic peptide amide kappa opioid agonist patent portfolio is wholly owned by us. The portfolio includes ten 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 and 8,951,970) with claims to compositions of a wide range of synthetic peptide amide kappa opioid agonists, including CR845 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 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 patent portfolio also includes pending U.S. patent applications which claim additional uses and methods of administering CR845. 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, China, Hong Kong, Israel Japan, Malaysia, Mexico, New Zealand, Russia, Singapore, South Africa and South Korea. These granted foreign patents with claims to CR845 are due expire no earlier than November 12, 2027. Patent applications claiming CR845 are pending in Brazil and India and a Canadian application with claims covering CR845 has been allowed.

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; and a pending U.S. patent application claiming CR701, related compounds, and methods of using these compounds. 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 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 and has been allowed in Canada.

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 patent portfolio, which is wholly owned by us, includes U.S. Patent No. 5,965,701 claiming CR665, our first generation kappa opioid receptor agonist, related compounds, and methods of using these compounds. U.S. Patent No. 5,965,701 is due to expire no earlier than December 23, 2017. A related international PCT application was filed and 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 U.K. are due to expire December 22, 2018.

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 pain 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:

I.V. CR845 – Acute Pain. We are developing I.V. CR845 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 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. Additionally, numerous companies are developing additional product candidates for the treatment of acute postoperative pain.

I.V. CR845 - Uremic Pruritus. We are developing I.V. CR845 for the management of uremic pruritus in hemodialysis patients. Currently, there are no approved products for management of uremic pruritus in the United States. However, there are many products that are being tried to help manage uremic pruritus. The most common agents tried 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 uremic pruritus, there are several companies involved in the discovery, development, and/or marketing of such products. Such product candidates include nalbuphine, asimadoline and nalfurafine.

Oral CR845. We are developing Oral CR845 for the management of moderate-to-severe acute and chronic pain. The market for the management of moderate-to-severe acute and 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 Actavis; NUCYNTA ER, an extended release formulation of tapentadol 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.

CR701. We plan to develop CR701 for neuropathic pain indications such as postherpetic neuralgia, or PHN, and neuropathic pain associated with diabetic peripheral neuropathy, or DPN. If approved for marketing, CR701 will compete against more established products that have been approved for treatment of various neuropathic pain indications. One of the most widely-prescribed drug in the United States for treatment of neuropathic pain is gabapentin, which is marketed by Pfizer and is also available generically. Gralise, a once-daily tablet formulation of gabapentin for the treatment of PHN, is marketed by Depomed. Pfizer markets Lyrica, an oral anticonvulsant, for use in the treatment of PHN and neuropathic pain associated with DPN. Janssen Pharmaceuticals markets Nucynta, an extended-release mu opioid tablet, for neuropathic pain associated with DPN. Topical prescription products currently marketed in the United States for neuropathic pain indications include Lidoderm, a lidocaine patch marketed by Endo Pharmaceuticals for PHN, and Qutenza, a capsaicin patch marketed by Acorda Therapeutics for PHN.

In addition to the foregoing products and product candidates, a number of products that are approved for treatment of other diseases are used by physicians to treat PHN, and it is possible that other such products will be shown to exhibit efficacy in the future and thereby emerge as competitors to CR701 for the treatment of different types of neuropathic pain. There are many other companies working to develop new drugs and other therapies to treat neuropathic pain.

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, Oral CR845 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 also 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 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 business associates. 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 Payment 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, imprisonment, exclusion from participation in government healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement Generally

The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental payer programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payers provide coverage for and establish adequate reimbursement levels for our product candidates. In the United States, private health insurers and other third party payers often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services. In the United States, the European Union and other potentially significant markets for our product candidates, government authorities and third party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and utilization, which may adversely affect our future product sales and results of operations. For example, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. 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. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for our product candidates in whole or in part.

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, among other things, 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 full impact on our business is unclear as many of its reforms require the promulgation of additional detailed regulations implementing the statutory provisions which has not yet completely occurred. Further, there have been judicial and Congressional challenges to certain aspects of the Health Care Reform Law, and we expect there will be additional challenges and amendments in the future.

In addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. In August 2011, the President 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 research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $21.2 million, $15.1 million and $8.7 million in 2015, 2014 and 2013, respectively. We plan to increase our research and development expenses for the foreseeable future as we seek to complete the development of I.V. CR845 and Oral CR845 and advance the development of CR701.

Employees

As of December 31, 2015, we had 20 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 ("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 as an inactive textual reference only. 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 with a limited operating history. For the last several years, we have focused our efforts primarily on developing I.V. and Oral CR845 with the goal of achieving regulatory approval. We are presently on IND clinical hold for I.V. CR845. Since inception, we have incurred significant operating and net losses available to common stockholders. Our net losses available to common stockholders were $24.7 million, $17.7 million and $3.1 million for the years ended December 31, 2015, December 31, 2014 and December 31, 2013, respectively. As of December 31, 2015, we had an accumulated deficit of $104.9 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 and our other product candidates. 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 CKD, the receipt of payments under any future collaborations we may enter into, and our expenditures on other research and development activities.

In addition, we expect to incur significant sales, marketing and manufacturing expenses related to the commercialization of I.V. and Oral CR845 or our other product candidates, 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 substantially as we:

- continue our I.V. CR845 pivotal clinical trial program in acute pain;
- continue the development of our I.V. CR845 uremic pruritus product candidate;
- continue our Phase 2 clinical trials for Oral CR845 in acute and chronic pain;
- continue the research and development of CR701, our other product candidate, and any potential future product candidates;
- seek regulatory approvals for I.V. CR845 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 are only in the preliminary stages of most of these activities. 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 research and development 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 short 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. 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, 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 and our other future product candidates, if approved by the FDA;
- qualify and outsource the commercial-scale manufacturing of our products under cGMP;
- advance Oral CR845 beyond Phase 2 clinical trials;
- develop additional product candidates, including CR701; and
- in-license other product candidates.

We believe that with our available cash and cash equivalent and marketable securities balances as of December 31, 2015 we will have sufficient funds to meet our projected operating requirements until the end of the first quarter of 2018, 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 planned development of Oral CR845, 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, and any costs associated with such delays;
- the costs of establishing a commercial organization to sell, market and distribute I.V. CR845;
- the rate of progress and costs related to our Phase 2 development of Oral CR845;
- the rate of progress and costs of our efforts to prepare for the submission of an NDA for I.V. CR845, Oral CR845 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 in preparation for commercialization;
- 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 and our other 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, 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. Our business depends entirely on the successful development and commercialization of our product candidates, and in particular, I.V. CR845, 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. We currently generate no revenues from sales of any products, and we may never be able to develop or commercialize a marketable product.

We initiated the first pivotal clinical trial for I.V. CR845 in acute pain in the third quarter of 2015. As described elsewhere in this report, in February 2016, the FDA placed the trial on IND clinical hold pending a safety review following the triggering of a stopping rule in the trial protocol. In addition to this clinical development, I.V. CR845 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 I.V. CR845, 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, I.V. CR845, we will not be able to generate revenue from I.V. CR845 in the United States in the foreseeable future, or at all. Any significant delays in obtaining approval for and commercializing I.V. CR845 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 or any of our other product candidates will be successful in clinical trials or receive regulatory approval. Even though I.V. CR845 has completed three Phase 2 clinical trials and has begun its Phase 3 clinical trial program, 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 subsequent clinical trials, including our planned Phase 3 clinical trials. Further, our product candidates, including I.V. CR845, 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 I.V. CR845 will depend on our ability to:

- create market demand for I.V. CR845 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 in the United States;
- manufacture I.V. CR845 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 in foreign markets where we receive marketing approval;
- maintain patent and trade secret protection and regulatory exclusivity for I.V. CR845;
- launch commercial sales of I.V. CR845, whether alone or in collaboration with others;
- achieve market acceptance of I.V. CR845 by patients, the medical community and third-party payers;
- achieve coverage and adequate reimbursement for I.V. CR845;
- effectively compete with other therapies; and
- maintain a continued acceptable safety profile of I.V. CR845 following launch.

As we continue to develop our other product candidates, including Oral CR845 and CR701, 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.

Our lead product candidate, I.V. CR845, and our second product candidate, Oral CR845, 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 amongst 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 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 for acute postoperative pain and uremic pruritus and Oral CR845 for acute and chronic pain. 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 research and development 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.

If we fail to supply CR845 to our collaboration partners we could lose revenues and be in breach of our obligations.

In connection with our agreements with Maruishi and CKD, we are obligated to negotiate in good faith to enter into supply agreements, pursuant to which, subject to certain conditions, we have obligations to supply CR845

to these parties for commercialization. At this time, our suppliers for I.V. CR845 include Polypeptide Laboratories, or Polypeptide, for the active pharmaceutical ingredient, and Patheon UK Limited or Patheon, for manufacturing of the finished clinical trial material. We have developed a formulation of Oral CR845 based on proprietary technology of Enteris Biopharma, Inc., or Enteris. Under the terms of our agreement with Polypeptide, it has agreed to manufacture and supply to us quantities of active pharmaceutical ingredient according to mutually agreed upon specifications for clinical trial purposes. In addition, under the terms of our agreement with Patheon, we have agreed to supply Patheon with sufficient quantities of active pharmaceutical ingredient, which it in turn manufactures into clinical trial material for use in our clinical trials. 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. If we are unable to obtain an adequate supply of CR845 product from third-party suppliers to meet our obligations to Maruishi or CKD, we will be in breach of our supply obligations under the agreements, and may be liable for damages, which could also hurt our business and reputation. In addition, our failure to supply our partners with CR845 will inhibit their ability to commercialize CR845 products, which, in turn will result in a loss of revenue for us.

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 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 and Oral CR845, 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 pending IND clinical hold related to our ongoing adaptive pivotal trial of I.V. CR845, 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.

The FDA may determine that I.V. CR845, 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 pivotal trial of I.V. CR845 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. There can be no guarantee that the FDA will remove this clinical hold promptly or at all. If other concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical testing, including during the FDA's ongoing safety review related to I.V. CR845, 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 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 or any other product candidate.

To date, the side effects observed in the completed I.V. CR845 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 pivotal 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, 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, kappa opioid agonists, the class of drugs that I.V. CR845 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 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.

We may seek breakthrough therapy designation for I.V. CR845 for uremic pruritus, but even if it is granted, it may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that I.V. CR845 will receive marketing approval.

We may seek a breakthrough therapy designation for I.V. CR845 for uremic pruritus. 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.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe I.V. CR845 meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate 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, even if I.V. CR845 qualifies as a breakthrough therapy, 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.

We may seek orphan drug status for I.V. CR845 for uremic pruritus, but even if it is granted, we may be unable to maintain any benefits associated with orphan drug status, including market exclusivity.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States, or for which there is no reasonable expectation that the cost of developing and making available in the United States a drug or biologic for a disease or condition will be recovered from sales in the United States for that drug or biologic. If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity.

We may seek orphan drug status for I.V. CR845 for the treatment of uremic pruritus, although the FDA could decide not to grant orphan drug status, including if it were to determine that the uremic pruritus patient population in the United States exceeds 200,000. Moreover, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan designated indication and may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

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 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, and our second product candidate, Oral CR845, 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 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-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-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, or CSA, 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 may have the potential to be a Schedule V or non-scheduled peripheral opioid. However, while CR845-based products have not demonstrated any evidence of the euphoria that has led to misuse, abuse, and addiction of mu opioids, and while CR845-based products are not being treated as a controlled substance in clinical trials, it is possible that the DEA could determine that CR845-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 that 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 was determined that our product candidates are subject to these restrictions, the commercialization of our product candidates could be limited.

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, 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, injunctions or criminal prosecution, any of which could significantly harm our business.

Even if one of our CR845-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. 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, Depomed, Pacira and Pernix..

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. Generic products are currently on the market for 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 research and development, 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 is approved by the FDA, we plan to build a commercial infrastructure, including our own specialty sales force, to launch I.V. CR845 in 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 and Oral CR845 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 we are unable to develop a marketing and sales infrastructure, we may not be able to commercialize I.V. CR845 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 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 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 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 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. 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 or any of our other product candidates.

In the event 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 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. CR845 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, or any of our other product candidates, including Oral CR845, 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 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, and in particular I.V. CR845, 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 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 and/or chronic pain;
- 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 and any of our other product candidates 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 formularies, and our ability to obtain sufficient third-party coverage

or reimbursement. Generally, before we can attempt to sell I.V. CR845 in a hospital, I.V. CR845 must be approved for addition to that hospital's list of drugs approved for use in that hospital, or formulary list. In evaluating drugs for inclusion on the formulary list, hospitals evaluate a variety of factors, including cost. The frequency with which hospitals add and remove drugs from their formulary lists varies from hospital to hospital, and hospitals 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. 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. 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 pain management products for acute pain and over-the-counter alternatives for chronic pain may also limit acceptance of our product candidates among physicians, patients and third-party payers. If I.V. CR845, 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, 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 or other product candidates that we may develop and may have to limit their commercialization.

The use of I.V CR845 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;
- loss of revenues;
- 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, 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 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 clinical trials; Polypeptide for I.V. CR845 and Enteris for Oral CR845. 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, 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 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 in Japan. Also, in April 2012, we entered into an agreement with CKD under which we granted CKD an exclusive license to develop, manufacture and commercialize products containing CR845 in South Korea. Both Maruishi and CKD are required to use commercially reasonable efforts, at their expense, to develop, obtain regulatory approval for and commercialize CR845 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 CKD, 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 CKD to develop, manufacture and commercialize products containing CR845 (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 CKD agreements may be terminated by our collaborator for our breach or insolvency, Maruishi may terminate its agreement with us at will, and CKD 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 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 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 will require many third parties, over whom we have no control, to decide to utilize I.V. CR845 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 is approved by the FDA, before we can attempt to sell I.V. CR845 in a hospital, I.V. CR845 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 for use in their institutions will adversely impact their overall pharmacy budgets, which could cause pharmacists to resist efforts to add I.V. CR845 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 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.

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 penalty laws, including 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 Medicare, Medicaid, or other third-party payers that are false or fraudulent;
- HIPAA, which created additional federal criminal statutes that prohibit 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;
- 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, diminished profits and future earnings, 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 or any of our other product candidates, if any, or if hospitals 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. 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. Accordingly, I.V. CR845 or any of our other product candidates, if approved, will face competition from other therapies and drugs for these limited hospital 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, the President 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 Payment 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;
- creation of the Independent Payment Advisory Board which will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations;
- 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.

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, 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, and reform government program reimbursement methodologies for drugs. 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.

These measures could result in decreased net revenues from our pharmaceutical products and decrease potential returns from our development efforts. Many of the details regarding the implementation of the Health Care Reform Law are yet to be determined, there have been judicial and Congressional challenges to certain aspects of the Health Care Reform Law, and we expect that there will be additional challenges and amendments. Thus, the full effect that the Health Care Reform Law would have on our business remains unclear.

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 significant fines or other sanctions.

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 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 research and development 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 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 recently 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, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our 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 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-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 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 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 or our other product candidates may infringe. There could also be existing patents of which we are not aware that I.V. CR845 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 product candidate can be challenged by competitors.

If I.V. CR845 is approved by the FDA, one or more third parties may challenge the patents covering this product candidate, 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, 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; (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, 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, Managing Growth

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

As of December 31, 2015, we had 20 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, if approved. Our management, 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, 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, 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 3, 2016, our stock price has been volatile, trading at prices ranging from $4.26.to $23.61, 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:

- developments regarding our pending IND clinical hold related to our ongoing adaptive pivotal clinical trial for I.V. CR845;
- delays in the commencement, enrollment and ultimate completion of Phase 3 clinical trials for I.V. CR845;
- any delay or refusal on the part of the FDA in approving an NDA for I.V. CR845 or our other product candidates;
- the commercial success of I.V. CR845 or our other product candidates, if approved by the FDA;
- results of clinical trials of I.V. CR845 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, Oral CR845 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 or our other product candidates, which would likely further delay any such approval;
- if I.V. CR845 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 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, our other product candidates, or the product candidates of our competitors; and
- if I.V. CR845 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 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.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. As of March 3, 2016, we had approximately 27.3 million shares of our common stock outstanding. In addition, certain holders of shares of our common stock may require us, subject to certain conditions, to prepare and file a registration statement under the Securities Act of 1933, as amended, or the Securities Act, and are entitled to include their shares in any registration statement we may file for ourselves or other stockholders. If we register the resale of these shares in the future, the holders could sell those shares freely in the public market, without regard to the limitations of Rule 144 under the Securities Act. We have also registered for offer and sale all shares of common stock that we may issue under our stock-based compensation plans. These shares can generally be freely sold in the public market upon issuance. Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise adequate capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

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 $1.0 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 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 research and development tax credits may expire and not be used. As of December 31, 2015, we had federal and state net operating loss carryforwards of approximately $95.9 million and

$89.9 million, respectively, and we also had federal and state research and development tax credit carryforwards of approximately $3.6 million and $0.7 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. To the extent 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 offering in 2015, 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.

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 be permitted to take actions by written consent;
- our stockholders are not be 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 53,000 square feet of leased office and laboratory space in Shelton, Connecticut pursuant to a lease agreement that expires in 2017.

In December 2015, we signed a lease agreement for approximately 24,000 square feet of office space in Stamford, Connecticut for the purpose of relocating our operating facility. The term of the lease begins on the date that renovations to the office space are completed, which is expected to be in May 2016, and ends 7.5 years thereafter. 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 21 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" and began trading on January 31, 2014, the day following the effective date of our initial public offering, or IPO. Prior to our IPO, there was no public market for our common stock.

Fiscal 2015	High	Low
First Quarter (January 1, 2015 to March 31, 2015)	$11.26	$ 9.00
Second Quarter (April 1, 2015 to June 30, 2015)	$13.32	$ 9.36
Third Quarter (July 1, 2015 to September 30, 2015)	$23.61	$11.66
Fourth Quarter (October 1, 2015 to December 31, 2015)	$18.12	$13.17

Fiscal 2014	High	Low
First Quarter (January 31, 2014 to March 31, 2014)	$23.25	$10.40
Second Quarter (April 1, 2014 to June 30, 2014)	$20.70	$12.51
Third Quarter (July 1, 2014 to September 30, 2014)	$17.77	$ 7.81
Fourth Quarter (October 1, 2014 to December 31, 2014)	$10.57	$ 7.53

The last reported sale price of our common stock as reported on The NASDAQ Global Market on March 3, 2016 was $5.64 per share.

Stockholders

As of March 3, 2016, there were 54 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.

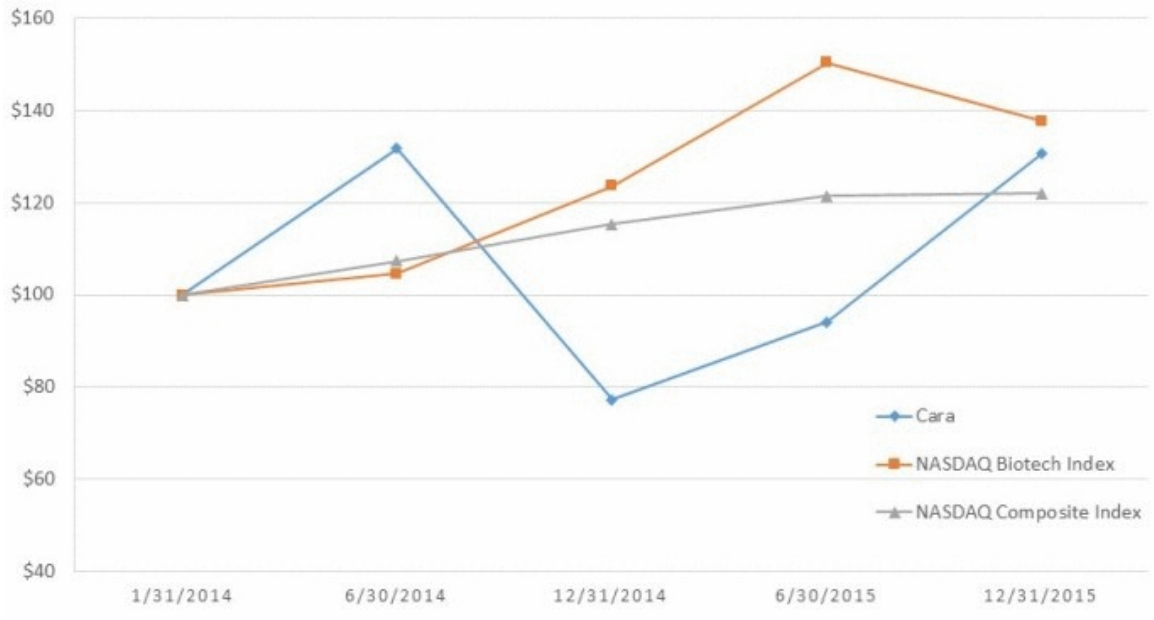
Dividend Policy

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 Market, 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 Global Market 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	6/30/2014	12/31/2014	6/30/2015	12/31/2015
Cara Therapeutics, Inc.	100	131.84	77.23	94.11	130.60
NASDAQ Composite	100	107.41	115.40	121.52	122.02
NASDAQ Biotechnology	100	104.55	123.71	150.45	137.83

This performance graph shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or incorporated by reference into any filing of ours under the Securities Act of 1933, as amended, or the Securities Exchange Act, except as shall be expressly set forth by specific reference to such filing.

Recent Sales of Unregistered Securities

Not applicable.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

Not applicable.

Use of Proceeds

On January 30, 2014, our registration statement on Form S-1 (File No 333-192230) was declared effective for our initial public offering, pursuant to which we registered the offering and sale of 5,750,000 shares of common stock, $0.001 par value per share (including 750,000 shares issued upon the underwriters' exercise of an option to purchase additional shares) at a public offering price of $11.00 per share for an aggregate public offering price of $63.3 million.

As a result of the initial public offering, we received net proceeds on February 5, 2014 of approximately $58.8 million from the sale of 5,750,000 shares of common stock, after deducting approximately $4.4 million of underwriting discounts and commissions but before giving effect to any offering expenses borne by us. In addition, we have paid approximately an additional $2.5 million of offering expenses in connection with our IPO. None of such payments were direct or indirect payments to any of (i) our directors or officers or their associates, (ii) persons owning 10 percent or more of our common stock, or (iii) our affiliates.

There has been no material change in the planned use of proceeds from our initial public offering from that described in the final prospectus related to the offering, which we filed with the Securities and Exchange Commission on February 3, 2014. As of December 31, 2015, we have used $24.8 million of the proceeds from our initial public offering for clinical trials and payments to research and development consultants.

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

The following selected financial data for the years ended December 31, 2015, December 31, 2014 and December 31, 2013 and as of December 31, 2015 and December 31, 2014 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, 2012 and December 31, 2011 and as of December 31, 2013, 2012 and 2011 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,				
	2015	2014	2013	2012	2011
	(in thousands, except share and per share data)				
Statement of Operations Data:					
Revenue:					
License and milestone fee revenue	$ 1,710	$ 302	$ 9,637	$ 1,190	$ —
Collaborative revenue	2,093	2,201	2,225	—	—
Clinical compound revenue	—	674	102	—	—
Total revenue (1)	3,803	3,177	11,964	1,190	—
Operating expenses:					
Research and development	21,221	15,068	8,685	4,597	7,159
General and administrative	7,770	6,181	3,516	2,829	2,407
Total operating expenses	28,991	21,249	12,201	7,426	9,566
Operating loss	(25,188)	(18,072)	(237)	(6,236)	(9,566)
Other income (expense), net (2)	101	126	(3,756)	(66)	(275)
Loss before benefit from income taxes	(25,087)	(17,946)	(3,993)	(6,302)	(9,841)
Benefit from income taxes	397	201	30	31	35
Net loss	$ (24,690)	$ (17,745)	$ (3,963)	$ (6,271)	$ (9,806)
Net loss available to common stockholders	$ (24,690)	$ (17,745)	$ (3,072)	$ (6,271)	$ (9,806)
Net loss per share available to common stockholders:					
Basic and Diluted	$ (1.00)	$ (0.85)	$ (0.74)	$ (1.90)	$ (3.03)
Weighted average shares:					
Basic and Diluted	24,620,372	20,965,935	4,133,138	3,299,993	3,235,743

	As of December 31,				
	2015	2014	2013	2012	2011
Balance Sheet Data:					
Cash and cash equivalents and marketable securities (3)	$ 106,740	$ 52,663	$ 12,357	$ 1,117	$ 4,097
Total assets	110,897	55,934	18,083	5,537	10,685
Deferred revenue	—	1,452	3,475	—	—
Total liabilities	5,853	4,272	6,572	3,098	4,581
Total convertible preferred stock (4)	—	—	65,586	58,522	58,168
Total stockholders' equity (deficit)	105,044	51,662	(54,075)	(58,133)	(52,064)

(1) The changes in revenue from the years ended December 31, 2011 through December 31, 2015 reflect upfront payments in connection with our entering into a license agreement with CKD in 2012 and a license agreement with Maruishi in 2013, continuing collaborative work with Maruishi in 2014 and 2015 and milestone payments earned under our collaborations with Maruishi in 2014 and 2015 and with CKD in 2015 (refer to the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations —Collaborations with Maruishi and CKD, Results of Operations" and Note 14 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 (refer to Note 9 of Notes to Financial Statements, *Convertible Promissory Notes,* in this Annual Report on Form 10-K).

(3) The increase in cash and cash equivalents and marketable securities from 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 August 4, 2015, and the proceeds from our IPO, which closed on February 5, 2014, respectively (refer to Note 12 of Notes to Financial Statements, *Stockholders' Equity,* in this Annual Report on Form 10-K). The increase in cash and cash equivalents and marketable securities from December 31, 2012 to December 31, 2013 primarily reflects the sale of Junior A convertible preferred stock to Maruishi in June 2013 and the issuance of convertible promissory notes in February 2013 (refer to Note 14 of Notes to Financial Statements, *Collaborations,* and Note 9 of Notes to Financial Statements, *Convertible Promissory Notes,* respectively, 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 (refer to Note 11 of Notes to Financial Statements, *Convertible Preferred Stock*, in this Annual Report on Form 10-K).

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

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

Overview

Introduction

We are a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting kappa opioid receptors. We are developing a novel and proprietary class of product candidates that target the body's peripheral nervous system.

Our most advanced product candidate, I.V. CR845, demonstrated significant pain relief and a favorable safety and tolerability profile in three randomized, double-blind, placebo-controlled Phase 2 clinical trials in patients with acute postoperative pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics. In addition, in the fourth quarter of 2014, we successfully completed a Human Abuse Liability, or HAL, trial of I.V. CR845 in which I.V. CR845 met the primary endpoint of demonstrating statistically significant lower "drug liking" scores as compared to the approved schedule IV opioid, pentazocine. We believe that the totality of results from the HAL trial are supportive of the potential for CR845 to be the first non-scheduled or low scheduled (Schedule V) peripheral opioid for acute pain.

In April 2015, we completed an End-of-Phase 2 meeting with the FDA, to discuss the design of our pivotal trials for our I.V. CR845 product candidate in acute pain. In September 2015, we initiated our Phase 3 clinical trial program for I.V. CR845 in postoperative pain with the dosing of the first subjects in an adaptive pivotal 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 I.V. CR845 or placebo administered both prior to and following abdominal surgery in male and female patients. The trial will enroll up to 600 patients undergoing either hysterectomy, prostatectomy, hemi-colectomy or ventral hernia, all of which are associated with moderate-to-severe postoperative visceral pain, at approximately 30 clinical sites within the United States. Three dose levels of I.V. CR845 (1.0, 2.0 and 5.0 ug/kg I.V.) will be compared to placebo, with an interim conditional power assessment to identify optimal doses that will be used to complete the enrollment of this study. The primary efficacy measure is the Change in Pain Intensity over the 24-hour postoperative period, or AUC-24, using the patient-reported Numeric Rating Scale, or NRS, score collected at pre-specified time points through 24 hours. Postoperative nausea and vomiting, or PONV, will be evaluated as a secondary efficacy measure. The impact of I.V. CR845 treatment on inflammatory biomarkers will also be explored.

In February 2016, the FDA advised us that our adaptive pivotal trial of I.V. CR845 for postoperative pain had been placed 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 that was included in the clinical trial protocol. Four patients out of 90 total patients dosed to date, all of whom were in the highest I.V. CR845 dose group (5 ug/kg), exhibited transient serum sodium levels equal to or greater than 150 mmol/L. All four patients were asymptomatic and sodium levels resolved to normal levels (less than 146 mmol/L) within 24 hours post-dosing with standard fluid management. No patients in the other two dose groups (2 ug/kg and 1 ug/kg) exhibited serum sodium levels greater than 150 mmol/L. A review of unblinded safety data has been undertaken by both us and the Independent Data Monitoring Committee in accordance with the clinical trial protocol.

The most common adverse events (> 5%) reported across treatment groups and placebo so far were nausea, hypernatremia, abdominal distension and procedural hypotension. All cases of abdominal distension and procedural hypotension were attributed to the surgical procedure and not to study drug. There were no cases of respiratory depression, no adverse events greater than Grade 1, and no CR845-associated serious adverse events have been reported. We anticipate continuing the trial following FDA review of the patient safety data and removal of the clinical hold.

Based on previous guidance from the FDA, we believe we will require 1,500 total exposures to I.V. CR845, including all Phase 1, Phase 2 and Phase 3 trials, prior to submitting a new drug application, or NDA. We believe our planned clinical trials and our clinical trials completed to date will result in a sufficient number of drug exposures to support an NDA.

We are also developing an oral version of CR845, or Oral CR845, for acute and chronic pain. In August 2015, we advanced our tablet formulation of Oral CR845 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, pharmacokinetics, or PK, and effectiveness of oral CR845 tablets dosed over a two-week treatment period in OA patients experiencing moderate-to-severe pain, defined as >4 on an 11-point NRS at baseline. 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 enrolled at five sites in the United States. In addition to safety and PK observations, CR845's effectiveness was assessed by: change from baseline in joint pain using the Numeric Rating Scale, or NRS, which was measured daily, change from baseline in the Western Ontario and McMaster Osteoarthritis Index, or WOMAC, which was measured at the end of Weeks 1 and 2 of treatment, change from baseline in rescue medication use, measured daily, and Patient Global Assessment, or PGA, which was measured on the last day of the study. Acetaminophen was the only allowable rescue medication. PK analyses indicated dose-proportional exposure of CR845 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 show a dose-related reduction in mean baseline pain score up to 34% after two weeks, with statistically significant reduction in mean rescue medication for the top 5.0 mg dose group of approximately 80 percent (ANOVA: 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 (Cochran-Mantel-Haenszel test, p=0.02, 2-sided). In this trial, all four tablet strengths were observed to be safe and well tolerated. The Phase 2a trial establishes therapeutic doses and a dosing regimen for a larger double-blind, placebo-controlled Phase 2b trial, which we plan to conduct during the second half of 2016.

CR845 has exhibited anti-pruritic, or anti-itch, potency in standard preclinical models. In the fourth quarter of 2014, we reported positive top-line dose-ranging PK and safety data from a Phase 1b clinical trial, which was part A of a Phase 2 proof-of-concept trial, of I.V. CR845 for the treatment of uremic pruritus, a systemic condition with high prevalence in dialysis patients, for which there are no approved therapeutics in the United States. In July 2015, we reported positive top-line efficacy results from Part B of this Phase 2 proof-of-concept trial, in which we observed that I.V. CR845 demonstrated statistically significant results on the primary endpoint of reducing worst itch intensity as well as the secondary endpoint of quality of life improvements**.** We also observed I.V. CR845 to have a favorable safety and tolerability profile in the trial.

Based on the results of this trial, during the fourth quarter of 2015 we completed a guidance meeting with the FDA, the outcome of which will guide the overall design of our Phase 3 clinical trial program for I.V. CR845 for the treatment of uremic pruritus. Subject to the feedback from the FDA, we intend to initiate a first Phase 2/3 adaptive pivotal trial in uremic pruritus in the first half of 2016.

See *Part I, Item 1, Business – Our Product Candidates* in this Annual Report on Form 10-K for a more detailed discussion of our clinical trials.

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.

Since our inception and through December 31, 2015, we have received (1) net proceeds of $75.2 million from the sale of approximately 4.33 million shares of our common stock in a follow-on offering, which closed in August 2015, after deducting underwriting discounts and commissions and offering expenses paid by us (see Note 12 of Notes to Financial Statements, *Stockholders' Equity*, elsewhere in this Annual Report on Form 10-K); (2) $56.3 million from the sale of 5.75 million shares of our common stock in our IPO, after deducting underwriting discounts and commissions and offering expenses paid by us; (3) net proceeds of $65.9 million from the sale of various series of our convertible preferred stock, (4) $3.6 million from the issuance of our convertible promissory notes and (5) $3.8 million from the issuance of long-term debt.

In addition to our financing activities, we have received aggregate payments of $32.5 million pursuant to license agreements with Maruishi Pharmaceutical Co., Ltd., or Maruishi, in Japan and Chong Kun Dang Pharmaceutical Corporation, or CKD, in South Korea (see the section titled "Collaborations with Maruishi and CKD", below), related to CR845 and an earlier product candidate for which development efforts ceased in 2007.

Since inception, we have incurred significant operating and net losses available to common stockholders. Our net losses available to common stockholders were $24.7 million, $17.7 million and $3.1 million for the years ended December 31, 2015, December 31, 2014 and December 31, 2013, respectively. As of December 31, 2015, we had an accumulated deficit of $104.9 million. We expect to continue to incur significant expenses and operating and net losses over at least the next several years. 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 CKD, the receipt of payments under any future collaborations we may enter into, and our expenditures on other research and development activities.

We anticipate that our expenses will increase substantially as we:

- continue our I.V. CR845 pivotal clinical trial program in acute pain;
- continue the development of our I.V. CR845 uremic pruritus product candidate;
- continue the research and development of our Oral CR845 and other product candidates;
- seek regulatory approvals for I.V. CR845 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.

Collaborations with Maruishi and CKD

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

In April 2013, we entered into a license agreement with Maruishi (the "Maruishi Agreement") under which we granted Maruishi an exclusive license to develop, manufacture and commercialize drug products containing CR845 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 in the United States and Japan, respectively. In addition, we have provided Maruishi specific clinical development services for CR845 in Maruishi's field of use.

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 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 in Japan for uremic pruritus. 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 in Japan, if any, and share in any sub-license fees. In addition, in connection with the Maruishi Agreement, Maruishi purchased 2,105,263 shares of our Junior A Preferred Stock for $3.80 per share, for an aggregate purchase price of $8.0 million, which shares were automatically converted into 842,105 shares of common stock upon the closing of our initial public offering.

In April 2012, we entered into a license agreement with CKD (the "CKD Agreement") under which we granted CKD an exclusive license to develop, manufacture and commercialize drug products containing CR845 in South Korea. We and CKD are each required to use commercially reasonable efforts, at our respective expense, to develop, obtain regulatory approval for and commercialize CR845 in the United States and South Korea, respectively.

Under the terms of the CKD 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. We also issued 173,611 shares of our Junior Preferred Stock to CKD in consideration for $0.4 million, which shares were automatically converted into 69,444 shares of common stock upon the closing of our initial public offering. During 2012, we received $0.6 million, net of foreign taxes, from CKD upon the achievement of clinical development milestones under the CKD Agreement. In July 2015 and September 2015, we met the milestone criteria, as set forth in the CKD Agreement, for completion of a Phase 1b trial of Oral CR845 in the United States and for completion of a Phase 2 trial of CR845 in uremic pruritus patients in the United States, respectively. As a result, in August 2015 and October 2015, we received milestone payments of $0.2 million (net of South Korean withholding tax) and $0.4 million (net of South Korean withholding tax) from CKD. 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 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 payments under license agreements with Maruishi and CKD for CR845, a portion 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 $3.5 million in clinical development or regulatory milestone payments, net of contractual foreign currency adjustments and South Korean withholding taxes, but have not received any royalties, under these collaborations.

Research and Development

To date, our research and development expenses have related primarily to the development of CR845. Research and development expenses consist of expenses incurred in performing research and development activities, including compensation and benefits for full-time research and development employees, facilities expenses, including laboratory build-out costs, overhead expenses, cost of laboratory supplies, clinical trial and related clinical manufacturing expenses, third-party formulation expenses, fees paid to contract research organizations, or CROs, and other consultants, stock-based compensation for research and development employees and non-employee consultants and other outside expenses. Our research and development expenses also include expenses related to preclinical activities, such as drug discovery, target validation and lead optimization for CR845 and our other, earlier stage programs.

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

Research and development 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. We expect our research and development expenses to increase significantly over the next several years as we seek to progress I.V. CR845 through Phase 3 trials in acute pain and the FDA approval process, and as we continue our development efforts for I.V. CR845 in uremic pruritus and Oral CR845 in OA. 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, business development and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees, insurance costs and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future to support our continued research and development activities and potential commercialization of our product candidates and the increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, as well as insurance and investor relations costs. In addition, if I.V. CR845 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 (Expense), Net

Other income (expense), net, consists of interest income earned on our cash, cash equivalents, marketable securities and restricted cash and realized gains and losses on the sale of marketable securities, as offset by interest paid on debt instruments, amortized deferred financing costs and amortized debt discount. The debt discount primarily consists of the intrinsic value of the beneficial conversion feature embedded in the convertible promissory notes we issued in December 2012 and February 2013. All convertible promissory notes were either converted to shares of series D convertible preferred stock or repaid prior to December 31, 2013.

Benefit from Income Taxes

The benefit from income taxes relates to state research and development tax credits exchanged for cash pursuant to the Connecticut Research and Development Tax Credit Exchange Program, which permits qualified small businesses engaged in research and development activities within Connecticut to exchange their unused research and development 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, 2015, 2014 and 2013

	Year Ended December 31,				
	2015		2014		2013
		Dollar amounts in thousands			
		% change		% change	
License and milestone fee revenue	$1,710	466%	$ 302	-97%	$ 9,637
Collaborative revenue	2,093	-5%	2,201	-1%	2,225
Clinical compound revenue	—	-100%	674	561%	102
Total revenue	$3,803	20%	$3,177	-73%	$11,964

License and milestone fee revenue

License and milestone fee revenue consists of (1) for the year ended December 31, 2015, $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 CKD Agreement in July and September 2015; (2) for the year ended December 31, 2014, $0.3 million of the $0.5 million milestone achieved under the Maruishi Agreement, which was attributable to a previously delivered license; and (3) for the year ended December 31, 2013, $9.6 million from the upfront payment under the Maruishi Agreement, which was entered into in April 2013.

Collaborative revenue

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. Collaborative revenue for each of the years ended December 31, 2014 and 2013 includes $2.2 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, 2015, 2014 and 2013 includes $0, $0.6 million and $0.1 million, respectively, from the sale of clinical compound to Maruishi.

Research and Development Expense

	Year Ended December 31,				
	2015		2014		2013
	Dollar amounts in thousands				
		% change		% change	
Direct preclinical studies and clinical trial costs	$13,560	34%	$10,099	82%	$5,542
Consultant services in support of preclinical studies and clinical trials	999	-8%	1,091	394%	221
Stock-based compensation	1,073	208%	349	388%	71
Depreciation and amortization	447	6%	422	-1%	426
Other R&D operating expenses	5,142	65%	3,107	28%	2,425
Total R&D expense	$21,221	41%	$15,068	73%	$8,685

For the year ended December 31, 2015 compared to the year ended December 31, 2014, the net increase in direct preclinical studies and clinical trial costs and related consultant costs primarily resulted from increases totaling $5.4 million for the I.V. CR845 Phase 2/3 adaptive study and the Phase 2a Oral CR845 study in patients with OA and a net increase of $1.4 million of CR845 drug manufacturing costs. Those costs were partially offset by decreases totaling $4.0 million in clinical trial costs in connection with the I.V. CR845 HAL trial and the Oral CR845 Phase 1a/1b trials. There was also a net increase of $0.6 million of preclinical costs. The increase in stock-based compensation expense mostly reflects additional grants to more employees. 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, recruiting costs and the cost of meetings and travel.

For the year ended December 31, 2014 compared to the year ended December 31, 2013, the net increase in direct preclinical studies and clinical trial costs and related consultant costs primarily resulted from increases totaling $5.2 million for the Phase 1 Oral CR845 trial, the Phase 2 I.V. CR845 uremic pruritus trial and the I.V. CR845 HAL trial and a net increase of $2.6 million of CR845 drug manufacturing costs. Those increases in costs were partially offset by a decrease of $2.0 million in clinical trial costs in connection with the Phase 2 I.V. CR845 bunionectomy trial and the Phase 1 I.V. CR845 renal impairment trial. The increase in stock-based compensation expense reflects the granting of stock options in 2014, whereas there were no such grants in 2013. The increase in other R&D operating expenses was primarily the result of increases in payroll and related costs associated with R&D personnel and the cost of clinical compound sold to Maruishi as Maruishi increased its clinical trial activity in Japan.

The following table summarizes our research and development expenses by product candidate for the years ended December 31, 2015, 2014 and 2013:

	Year Ended December 31,				
	2015		2014		2013
	Dollar amounts in thousands				
		% change		% change	
External research and development expenses:					
I.V. CR845	$ 9,149	25%	$ 7,369	84%	$3,995
Oral CR845	5,402	24%	4,371	139%	1,826
Internal research and development expenses	6,670	99%	3,328	16%	2,864
Total research and development expenses	$21,221	41%	$15,068	73%	$8,685

General and Administrative Expense

	Year Ended December 31,				
	2015		2014		2013
	Dollar amounts in thousands				
		% change		% change	
Professional fees and public/investor relations	$1,883	6%	$1,773	8%	$1,639
Stock-based compensation	1,441	41%	1,022	1876%	52
Depreciation and amortization	392	9%	361	0%	363
Other G&A operating expenses	4,054	34%	3,025	107%	1,462
Total G&A expense	$7,770	26%	$6,181	76%	$3,516

For the year ended December 31, 2015 compared to the year ended December 31, 2014, the increase in professional fees and public/investor relations costs primarily included increases in public/investor relations costs, in legal fees and in accounting and auditing fees. Those increases were partially offset by decreases in consultant fees and patent costs. The increase in stock-based compensation expense primarily reflects additional grants to more employees and members of our Board of Directors than in the same period in 2014. The increase in other G&A operating expenses included increases in payroll and related costs, in connection with increased headcount, and in insurance costs.

For the year ended December 31, 2014 compared to the year ended December 31, 2013, the increase in professional fees and public/investor relations costs included increases in directors' fees as a result of our becoming a public company. Those increases were partially offset by decreases in consultant costs, primarily related to the success fee we incurred in connection with entering into the Maruishi Agreement in 2013, and decreased accounting and auditing fees, which were higher in 2013 in preparation for our initial public offering. Stock-based compensation expense increased due to the granting of stock options in 2014 in connection with the IPO. The increase in other G&A operating expenses included increases in payroll and related costs and directors' and officers' insurance costs, both as a result of our becoming a public company.

Other Income (Expense), net

Year Ended December 31,				
2015		2014		2013
Dollar amounts in thousands				
	% change		% change	
$101	-20%	$126	-103%	$(3,756)

During 2015, there was $101 thousand of interest income and dividends earned on our cash and cash equivalents, marketable securities and restricted cash. The decrease in interest income from the year ended December 31, 2014 was due to lower interest rates on a higher average balance in 2015.

During 2014, there was $126 thousand of interest income earned on our cash and cash equivalents and restricted cash. The decrease in interest expense from the year ended December 31, 2013 was due to the conversion of the outstanding convertible promissory notes during 2013.

The 2013 period includes $3.7 million of non-cash expenses in connection with the convertible promissory notes, including the accretion of debt discount relating to the intrinsic value of the beneficial conversion feature embedded in the notes and amortization of deferred financing costs, and accrued interest expense on the convertible promissory notes we issued in December 2012 and February 2013.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception and through December 31, 2015, we have raised an aggregate of approximately $237.5 million to fund our operations, including (1) proceeds of $75.2 million, net of underwriting discounts and commissions and offering expenses paid by us from our follow-on offering of our common stock, which closed in August 2015; (2) proceeds of $56.3 million, net of underwriting discounts and commissions and offering expenses paid by us, from our IPO, which closed in February 2014; (3) $32.5 million under our license agreements, primarily with Maruishi and CKD, and an earlier product candidate for which development efforts ceased in 2007; (4) proceeds of $65.9 million from the sale of shares of our convertible preferred stock, including Junior A convertible preferred stock; and (5) $7.4 million of net proceeds from debt financings, including convertible promissory notes and the Connecticut Innovations, Inc. Term Loan, described below. As of December 31, 2015, we had $106.7 million in unrestricted cash and cash equivalents and available-for-sale marketable securities, which we expect will be sufficient to fund our planned operating expenses and capital expenditure requirements through the end of the first quarter of 2018, without giving effect to any potential milestone payments we may receive under our collaboration agreements with Maruishi and CKD.

In order to fund future operations, including our planned clinical trials, we filed a shelf registration statement on Form S-3 (File No. 333-203072), which the Securities and Exchange Commission ("SEC") declared effective on May 13, 2015. This shelf registration statement provides for aggregate offerings of up to $150 million of common stock, preferred stock, debt securities, warrants or any combination thereof. On August 4, 2015, we completed a follow-on public offering of 4,327,956 shares of our common stock, including 564,516 shares sold pursuant to the full exercise by the underwriters of their option to buy additional shares, pursuant to this shelf registration statement and a related prospectus supplement dated July 29, 2015, filed with the SEC on July 30, 2015. We received gross proceeds from the offering of approximately $80.5 million, or net proceeds of $75.2 million after deducting the underwriting discounts and commissions and offering expenses paid by us. We may offer additional securities under this 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 this shelf registration statement provides us with the flexibility to raise additional capital to finance our operations as needed.

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 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 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 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 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.

Under the CKD Agreement, we are potentially eligible to earn up to an aggregate of $2.3 million in clinical development milestones and $1.5 million in regulatory milestones 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 in South Korea, if any, and share in any sub-license fees.

During the third quarter of 2015, we met the milestone criteria, as defined in the CKD Agreement, for both completion of a Phase 1b trial of Oral CR845 in the United States and completion of a Phase 2 trial of CR845 in the United States for the treatment of uremic pruritus, for which we earned clinical development milestone payments totaling $626 thousand, net of South Korean withholding tax of $124 thousand.

The next potential milestone payment that we could be entitled to receive under the Maruishi Agreement will be for a clinical development milestone for completion by us in the United States of the first Phase 3 pivotal trial of CR845 in acute pain. If achieved, this milestone will result in a payment of $1.0 million, before any foreign exchange adjustment, being due to us. The next potential milestone payment that we could be entitled to receive under the CKD Agreement will be for a clinical development milestone for completion of a Phase 3 trial of CR845 in the United States for 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 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.

Junior A Convertible Preferred Stock

Under the terms of the Maruishi Agreement, during April 2013, Maruishi purchased 2,105,263 shares of our Junior A convertible preferred stock pursuant to a stock purchase agreement for a purchase price of $8.0 million. These shares were recorded at their fair value of $7.7 million. As a result, the premium of $0.3 million was allocated to the arrangement consideration and was, therefore, recognized as license fee revenue in accordance with our revenue recognition policies. Upon closing of our IPO, all shares of Junior A convertible preferred stock were automatically converted to shares of our common stock.

Convertible Promissory Notes

In December 2012 and February 2013, we issued an aggregate of $4.0 million principal amount of convertible promissory notes due August 28, 2013. The notes bore interest at 8% per annum and included both optional and mandatory conversion features. The optional conversion feature allowed each note holder, at any time prior to maturity, to elect to convert the balance of the note plus accrued interest into shares of our Series D Convertible Preferred Stock at a conversion price of approximately $1.44 per share. The mandatory conversion feature of the notes provided that, if we issued or sold equity securities of not less than $10.0 million on or before the maturity date, the notes plus all accrued interest thereon would automatically convert into shares of the issued class of equity securities at a price per share equal to 90% of the cash price paid by the investors in the new equity securities.

We did not need to complete an equity financing prior to August 28, 2013, which would have triggered the mandatory conversion of the notes. In August 2013, certain holders of notes elected to convert their notes in the aggregate amount of $3.9 million in principal plus accrued interest into 2,692,291 shares of Series D Preferred Stock. In October 2013, we repaid the remaining notes in the aggregate amount of $311 thousand in principal and accrued interest thereon.

Connecticut Innovations, Inc. Term Loan

In September 2007, we entered into a $4.0 million term loan with Connecticut Innovations, Inc., or CII. The loan bore interest at a 7.0% rate and was payable in monthly installments over five years. In connection with the loan, we also issued a warrant to CII to purchase 19,851 shares of our common stock at an exercise price of $10.08. In September 2012, we amended the terms of the loan to defer all payments due between July 1, 2012 and December 31, 2012 until January 2, 2013 and to increase the interest rate on the loan to 8.5%. We repaid the outstanding amount of $307 thousand under the loan from CII, including accrued interest, in April 2013. On July 31, 2014, CII exercised its outstanding warrant to purchase 19,851 shares of our common stock, in a cashless exercise, resulting in the issuance of 6,383 shares of our common stock.

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, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs. See Part II Item 5, *Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities - Use of Proceeds* in this Annual Report on Form 10-K regarding the use of the net proceeds from our IPO.

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, Oral CR845 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. 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, Oral CR845 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 and preclinical 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 CKD.

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 Oral CR845 and I.V. CR845 in uremic 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: (1) completing required trials for I.V. CR845 in postoperative pain to enable an NDA submission; (2) completing a Phase 2b trial of Oral CR845 in chronic pain; and (3) advancing our CR845 uremic pruritus program through a Phase 2/3 adaptive pivotal trial, we expect that our existing cash and cash equivalents and available-for-sale marketable securities as of December 31, 2015 will be sufficient for us to fund our operating expenses and capital expenditure requirements through the end of the first quarter of 2018, without giving effect to any potential milestone payments we may receive under our collaboration agreements with Maruishi and CKD. 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.

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, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Net cash (used in) provided by operating activities	$(21,478)	$(17,642)	$ 2,829
Net cash used in investing activities	(91,677)	(42)	(5)
Net cash provided by financing activities	75,593	57,990	8,416
Net increase (decrease) in cash and cash equivalents	$(37,562)	$ 40,306	$11,240

Net cash (used in) provided by operating activities

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 operating activities for the year ended December 31, 2014 consisted primarily of a net loss of $17.7 million and a $1.8 million outflow from net changes in operating assets and liabilities, partially offset by $1.9 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 $1.4 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 $2.0 million decrease in deferred revenue from the Maruishi Agreement and a $0.1 million cash outflow related to income tax receivable. Those cash outflows were partially offset by a cash inflow of $0.4 million from a decrease in prepaid expenses, primarily related to decreases in prepaid clinical costs.

Net cash provided by operating activities for the year ended December 31, 2013 consisted primarily of a net loss of $4.0 million, offset by $4.4 million of net non-cash charges and a $2.4 million cash inflow from net changes in operating assets and liabilities. Net non-cash charges primarily consisted of $3.6 million of aggregate non-cash interest and amortization of beneficial conversion feature on our convertible promissory notes, depreciation and amortization expense of $0.8 million, amortization of deferred financing costs of $0.1 million and $0.1 million of stock-based compensation expense. Those increases were partially offset by deferred rent costs of $0.2 million. The net change in operating assets and liabilities primarily consisted of cash inflows from a $3.5 million increase in deferred revenue from the Maruishi Agreement and a $0.7 million increase in accounts payable and accrued expenses, partially offset by a cash outflow of $1.7 million, primarily related to costs of our IPO included in prepaid expense.

Net cash used in investing activities

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 used in investing activities for the years ended December 31, 2014 and 2013 related to the purchase of office equipment and furniture.

Net cash provided by financing activities

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.

Net cash provided by financing activities for the year ended December 31, 2014 consisted primarily of gross proceeds of $63.3 million from our IPO, partially offset by $5.5 million of underwriting discounts and commissions and offering expenses paid by us during the year ended December 31, 2014, proceeds of $0.1 million received from stock option exercises and proceeds of $0.1 million from the sale of our common stock to our Chief Medical Officer.

Net cash provided by financing activities for the year ended December 31, 2013, consisted primarily of $7.6 million of net proceeds from the sale of Junior A Convertible Preferred Stock to Maruishi and $1.4 million of net proceeds received on the issuance of convertible promissory notes, partially offset by the $0.3 million final principal payment under our loan agreement with CII and $0.3 million related to repayment of convertible promissory notes.

Contractual Obligations

The following table summarizes our significant contractual obligations as of December 31, 2015 (in thousands).

	Payment Due for the Year Ending December 31,						
	2016	2017	2018	2019	2020	Thereafter	Total
Shelton operating lease (1)	$ 913	$ 740	$ —	$ —	$ —	$ —	$ 1,653
Stamford operating lease (2)	288	875	1,093	1,217	1,241	3,650	8,364
	$1,201	$1,615	$1,093	$1,217	$1,241	$ 3,650	$10,017

(1) We lease our operating facility located in Shelton, Connecticut (see Note 21 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K).

(2) In December 2015, we signed a lease for office space in Stamford, Connecticut for the purpose of relocating our operating facility as of May, 2016 (see Note 21 of Notes to Financial Statements, *Commitments and Contingencies*, in this Annual Report on Form 10-K).

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 Generally-Accepted Accounting Principles in the United States ("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 research and development 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 ("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 stand-alone 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 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 uses 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. 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.

Arrangement consideration allocated to research and development 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. We have determined that our research and developments services deliverables, as applicable, represent separate units of accounting because similar services are sold separately by other vendors.

In connection with arrangement consideration allocated to research and development services, our performance period estimates are principally based on projections of the scope, progress and results of our research and development 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* ("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 lives), (iv) expected dividend yield on our common stock, and (v) risk-free interest rates.

Prior to the effective date of the registration statement related to our initial public offering in January 2014, we utilized methodologies in accordance with the framework of the American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation* (the "Practice Aid") to determine the fair value of our common stock on any given date. Subsequently, the stock price input to the Black-Scholes model for each stock option granted is the closing price of our common stock as quoted on The NASDAQ Global Market on the grant date.

Expected volatility is based on an analysis of guideline companies, which is applied consistently from period to period, in accordance with ASC 718. The expected life of stock options granted to employees and non-employee directors is determined using the average of the vesting period and term, an accepted method for our option grants under the SEC's Staff Accounting Bulletin No. 107, *Share-Based Payment*. 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 options' expected lives. 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.

Stock-based compensation expense also includes an estimate, which is made at the time of grant of each award, of the number of awards that are expected to be forfeited. This estimate is based upon historical experience of the occurrence of forfeitures of prior awards that we have granted. We revise this estimate, if necessary, in subsequent periods as each award vests, if actual forfeitures differ from those estimates. To the extent that the actual forfeiture rate for an award is lower than the estimated forfeiture rate, additional compensation expense is recorded in the period that the award vests.

We account for options issued to non-employee consultants under ASC 505, *Equity-Based Payments to Non-Employees*. As such, the fair value of such options is periodically re-measured using the Black-Scholes model with the expected life of stock options granted to non-employees initially equal to the options' maximum contractual life of ten years. Under ASC 505, upon re-measurement of each award, income or expense is recognized during its vesting 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.

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 notes, commercial paper and obligations of the U.S. government and 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, meet the definition of a debt security in Accounting Standards Codification section 320-10-20. We consider our marketable securities to be available-for-sale and, accordingly, these investments are recorded at fair value with unrealized gains and losses generally recorded in accumulated other comprehensive income (loss) as a separate component of stockholders' equity. All 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, 2015, 2014 or 2013.

We estimate the fair values of our financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, other 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 its validation procedures, we did not adjust or override any fair value measurements provided by our pricing services as of December 31, 2015. While we believe 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.

Research and Development 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. Research and development expenses include, among other costs, salaries and other personnel-related costs, costs to conduct clinical trials, costs to manufacture product candidates and clinical supplies, laboratory supplies costs and facility-related costs. Non-refundable research and development 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.

Valuations of Debt and Equity Instruments

Preferred Stock Valuations

As described below, in connection with the issuance of the convertible promissory notes, we estimated the fair value of our Series D Preferred Stock as of the respective dates of the issuance of the notes. We also estimated the fair value of our Junior Preferred Stock and Junior A Preferred Stock as of their respective dates of issuance. We determined the fair values of preferred stock by using the guidance prescribed by the Practice Aid, and we believe the methodologies used are appropriate and the valuation results are representative of the fair values of our Series D Preferred Stock, Junior Preferred Stock and Junior A Preferred Stock, as applicable.

Convertible Promissory Notes

In December 2012 and February 2013, we issued an aggregate of $4.0 million principal amount of convertible promissory notes due August 28, 2013. The sale was consummated through two closings. The initial closing was on December 28, 2012 for $2.5 million in aggregate principal amount, and the final closing was on February 28, 2013 for $1.5 million in aggregate principal amount.

The notes accrued interest at an annual rate of 8%. In accordance with the terms of the notes, each note holder, any time prior to the maturity date, could elect to convert the balance of the note plus accrued interest into shares of our Series D Preferred Stock at a conversion price of $1.44 per share. In accordance with GAAP, we determined that the intrinsic value of the beneficial conversion feature embedded in the notes issued in the initial closing was approximately $2.0 million, based on the estimated fair value of the Series D Preferred Stock (see “Preferred Stock Valuations” above) as of December 31, 2012 of $2.61 per share. This intrinsic value was recorded as debt discount. We determined that the intrinsic value of the beneficial conversion feature of the notes issued in the final closing was $1.4 million, based on the estimated fair value of the Series D Preferred Stock as of February 28, 2013 of $2.81 per share, and recorded this amount as additional debt discount. The debt discount was accreted to interest expense over the term of the notes.

Prior to the maturity date of the notes, we received notice from note holders to convert notes in the aggregate amount of $3.9 million in principal plus accrued interest into 2,692,291 shares of Series D Preferred Stock, and the remaining notes in the aggregate amount of approximately $311 thousand in principal and accrued interest were repaid in October 2013. For the year ended December 31, 2013, we amortized $3.4 million of debt discount to interest expense.

The holders of preferred stock who did not participate in the convertible promissory note financing described above had their shares of preferred stock converted into common stock at their respective then applicable conversion rates. As a result, as of February 2013, 2,246,743 shares of preferred stock were converted into 959,545 shares of common stock. We determined that this conversion represented an extinguishment of the preferred stock under GAAP and, accordingly, recorded an $891 thousand gain on extinguishment within accumulated deficit which represented the difference between the carrying value of the preferred stock and the fair value of the common stock issued upon conversion.

Preferred Stock Issuances

In connection with collaboration agreements with Maruishi and CKD, we have issued equity securities to our collaborative partners at the time of entering into our license agreements with the counterparties. In each instance, we issued shares of a newly designated series of preferred stock. Due to the absence of an active market for these shares of preferred stock, we utilized methodologies in accordance with the framework of the Practice Aid to estimate the fair value of the shares issued to Maruishi and CKD as of the dates of issuance. Each valuation includes estimates and assumptions that require our judgment. These estimates include assumptions regarding future performance, including the probability of successful completion of preclinical studies and clinical trials and FDA approval of product candidates containing CR845, the probability and estimated time to complete financing and collaborative transactions. Significant changes to the key assumptions used in the valuations could result in different fair values of the preferred stock at the respective valuation dates.

In the Maruishi transaction, we received an upfront non-refundable, non-creditable license fee of $15.0 million. In addition to this upfront payment, Maruishi also purchased 2,105,263 shares of our newly designated Junior A Preferred Stock pursuant to a stock purchase agreement at a purchase price of $3.80 per share, for total consideration of $8.0 million. Subsequent to the agreement, we estimate that the fair value of the Junior A Preferred Stock was $3.64 per share at the date of issuance. Based on this valuation, we assigned a value to the Junior A Preferred Stock issued to Maruishi of $7.7 million. As a result, we allocated an additional $0.3 million to the values of the license and research and development services elements under the Maruishi license arrangement.

In the CKD transaction, we received an upfront non-refundable, non-creditable license fee $1.0 million and, as partial consideration, issued CKD 173,611 shares of our newly designated Junior Preferred Stock. Based on our estimated fair value of the shares of Junior Preferred Stock issued in the transaction of $2.04 per share, or the aggregate of $354 thousand, we recorded the remaining proceeds of $646 thousand as license revenue. In each instance, we accounted for the values allocated to the respective license arrangements in accordance with our revenue recognition policies described above.

Common Stock Valuation

Prior to our initial public offering in January 2014, due to the absence of an active market for our common stock, we utilized methodologies in accordance with the framework of the Practice Aid to estimate the fair value of our common stock at various reporting dates. Each valuation includes estimates and assumptions that require our judgment. These estimates include assumptions regarding future performance, including the probability of successful completion of preclinical studies and clinical trials and FDA approval of product candidates containing CR845, the probability and estimated time to complete financing and collaborative transactions. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date.

We did not issue shares of common stock, options or warrants to purchase common stock or, except as described above, any other instruments convertible into. common stock between January 1, 2012 and January 30, 2014, the effective date of our initial public offering, other than the issuance of common stock upon the exercise of outstanding stock options. However, we estimated the fair value of our common stock as of December 31, 2012 and December 31, 2013 for purposes of revaluing outstanding options held by non-employee consultants and adjusting compensation expense accordingly during the vesting period of those options as required by GAAP. We also estimated the fair value of our common stock as of February 28, 2013 for purposes of accounting for the conversion of preferred stock, as described above.

As with the valuations of our preferred stock described above, we estimated the fair value of our common stock as of these dates by incorporating the guidance prescribed by the Practice Aid. For our December 31, 2012 and 2013 valuations, we employed solely the income approach, as we determined that our conditions had changed significantly since our most recent equity financing such that use of the market approach would be inappropriate.

Recent Accounting Pronouncements

Please refer to *Note 2* of *Notes to Financial Statements* 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 notes, commercial paper and direct obligations of the U.S. government and government-sponsored entities, and in cash equivalents. As of December 31, 2015, we have invested $91.6 million of our cash reserves in such marketable securities. Those marketable securities include $49.7 million of investment grade debt instruments with an average interest rate of approximately 0.53% and maturities through September 2016 and $41.9 million of money market funds with an average interest rate of 0.26%. As of December 31, 2014, we had $52.7 million of interest-bearing money market accounts, classified as cash equivalents. 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 and we do not believe a change in interest rates would have a material impact on our financial statements. 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 the end of the period covered by this Annual Report on Form 10-K. Management 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. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of the end of the period covered by this report, our disclosure controls and procedures were effective in ensuring that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC, and is 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

Management of Cara Therapeutics, Inc. 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.

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, 2015. Based on the assessment, management has concluded that, as of December 31, 2015, 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, 2015 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. ***Other Information.***

None.

PART III

Item 10. ***Directors, Executive Officers and Corporate Governance.***

The information required by this item 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 2016 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 2016 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 2016 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 2016 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 2016 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.

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.

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+(3)	Services Agreement dated July 2, 2004 between the Registrant and Bio Diligence Partners, Inc., as amended to date.
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.

Exhibit No.	Description of Exhibit
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.
23.1†	Consent of Ernst & Young, LLP, independent registered public accounting firm.
31.1†	Certification of Chief Executive Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
31.2†	Certification of Chief Financial Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
32.1	Certifications of Chief Executive Officer and Chief Financial Officer of Cara Therapeutics, Inc. pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. (furnished herewith).
101.CAL	XBRL Taxonomy Extension Calculation Linkbase.
101.INS	XBRL Instance Document.
101.LAB	XBRL Taxonomy Extension Label Linkbase
101.PRE	XBRL Taxonomy Extension Presentation Linkbase.
101.SCH	XBRL Taxonomy Extension Schema Linkbase
101.DEF	XBRL Definition Linkbase Document.

\+ Indicates management contract or compensatory plan.
* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.
† 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 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.
(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 January 17, 2014 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.

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 10th day of March 2016.

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 10, 2016
/s/ JOSEF SCHOELL Josef Schoell	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 10, 2016
/s/ HARRISON BAINS Harrison Bains	Director	March 10, 2016
/s/ JEFFREY IVES Jeffrey Ives, Ph.D.	Director	March 10, 2016
/s/ DEAN SLAGEL Dean Slagel	Director	March 10, 2016
/s/ MARTIN VOGELBAUM Martin Vogelbaum	Director	March 10, 2016

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

We have audited the accompanying balance sheets of Cara Therapeutics, Inc. as of December 31, 2015 and 2014, and the related statements of comprehensive loss, convertible preferred stock and stockholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Cara Therapeutics, Inc. at December 31, 2015 and 2014, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Stamford, Connecticut
March 10, 2016

CARA THERAPEUTICS, INC.

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

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$ 15,101	$ 52,663
Marketable securities,	91,640	—
Income tax receivable	384	200
Interest receivable	80	—
Prepaid expenses	1,729	287
Total current assets	108,934	53,150
Property and equipment, net	1,263	2,084
Restricted cash	700	700
Total assets	$ 110,897	$ 55,934
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 5,268	$ 1,946
Deferred Revenue	—	1,452
Total current liabilities	5,268	3,398
Deferred lease obligation	585	874
Commitments and contingencies *(Note 21)*	—	—
Stockholders' equity:		
Preferred stock; $0.001 par value; 5,000,000 shares authorized at December 31, 2015 and December 31, 2014; zero shares issued and outstanding at December 31, 2015 and December 31, 2014	—	—
Common stock; $0.001 par value; 100,000,000 shares authorized at December 31, 2015 and December 31, 2014; 27,254,863 shares and 22,802,039 shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively	27	23
Additional paid-in capital	209,943	131,840
Accumulated deficit	(104,891)	(80,201)
Accumulated other comprehensive loss	(35)	—
Total stockholders' equity	105,044	51,662
Total liabilities and stockholders' equity	$ 110,897	$ 55,934

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,		
	2015	2014	2013
Revenue:			
License and milestone fees	$ 1,710	$ 302	$ 9,637
Collaborative revenue	2,093	2,201	2,225
Clinical compound revenue	—	674	102
Total revenue	3,803	3,177	11,964
Operating expenses:			
Research and development	21,221	15,068	8,685
General and administrative	7,770	6,181	3,516
Total operating expenses	28,991	21,249	12,201
Operating loss	(25,188)	(18,072)	(237)
Other income (expense), net	101	126	(3,756)
Loss before benefit from income taxes	(25,087)	(17,946)	(3,993)
Benefit from income taxes	397	201	30
Net loss	$ (24,690)	$ (17,745)	$ (3,963)
Net loss available to common stockholders:			
Basic and Diluted	$ (24,690)	$ (17,745)	$ (3,072)
Loss per share available to common stockholders:			
Basic and Diluted	$ (1.00)	$ (0.85)	$ (0.74)
Weighted average shares:			
Basic and Diluted	24,620,372	20,965,935	4,133,138
Other comprehensive loss, net of tax of $0:			
Unrealized gains (losses) on available for sale marketable securities	(35)	—	—
Total comprehensive loss	$ (24,725)	$ (17,745)	$ (3,072)

See Notes to Financial Statements.

CARA THERAPEUTICS, INC.

STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' (DEFICIT) EQUITY
(amounts in thousands, except share and per share data)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive (Loss)	Total Stockholders' (Deficit) Equity	Convertible Preferred Stock		Beneficial Conversion Feature on Convertible Promissory Notes
	Shares	Amount					Shares	Amount	Amount
Balance at December 31, 2012	3,328,698	$ 3	$ 1,248	$ (59,384)	$ —	$ (58,133)	26,636,118	$ 58,522	$ 2,050
Issuance of Junior A convertible preferred stock	—	—	—	—	—	—	2,105,263	7,642	—
Preferred stock converted to common shares	959,545	1	3,574	891	—	4,466	(2,246,743)	(4,466)	—
Convertible promissory notes converted to Series D preferred stock	—	—	—	—	—	—	2,692,291	3,888	—
Beneficial conversion feature on convertible promissory notes	—	—	—	—	—	—	—	—	1,382
Reclassification of beneficial conversion feature	—	—	3,432	—	—	3,432	—	—	(3,432)
Stock-based compensation expense	—	—	123	—	—	123	—	—	—
Net loss	—	—	—	(3,963)	—	(3,963)	—	—	—
Balance at December 31, 2013	4,288,243	4	8,377	(62,456)	—	(54,075)	29,186,929	65,586	—
Preferred stock converted to common shares	12,554,171	13	65,573	—	—	65,586	(29,186,929)	(65,586)	—
Sale of common stock in initial public offering ($11.00 per share), net of underwriting discounts and commissions and offering expenses of $6,953	5,750,000	6	56,291	—	—	56,297	—	—	—
Sale of common stock in a private placement ($8.74 per share)	11,442	—	100	—	—	100	—	—	—
Stock-based compensation expense	—	—	1,371	—	—	1,371	—	—	—
Shares issued upon exercise of stock options	191,800	—	128	—	—	128	—	—	—
Shares issued upon cashless exercise of warrants	6,383	—	—	—	—	—	—	—	—
Net loss	—	—	—	(17,745)	—	(17,745)	—	—	—
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 income (loss)	—	—	—	—	(35)	(35)	—	—	—
Balance at December 31, 2015	27,254,863	$ 27	$ 209,943	$ (104,891)	$ (35)	$ 105,044	—	$ —	$ —

See Notes to Financial Statements.

CARA THERAPEUTICS, INC.

STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,		
	2015	2014	2013
Operating activities			
Net loss	$(24,690)	$(17,745)	$ (3,963)
Adjustments to reconcile net loss to net cash (used in) provided by operations:			
Stock-based compensation expense	2,514	1,371	123
Change in fair value of liability under license agreement	—	—	(35)
Accrued interest and amortization of beneficial conversion feature on promissory notes	—	—	3,605
Loss on write-off of fixed assets	2	—	—
Depreciation & amortization	839	783	789
Amortization/accretion of available-for-sale securities	(18)	—	—
Deferred rent costs	(289)	(265)	(238)
Amortization of financing costs	—	—	117
Changes in operating assets and liabilities:			
Income tax receivable	(184)	(139)	(30)
Interest receivable	(80)	—	—
Prepaid expenses	(1,442)	388	(1,736)
Accounts payable and accrued expenses	3,322	(12)	722
Deferred revenue	(1,452)	(2,023)	3,475
Net cash (used in) provided by operating activities	(21,478)	(17,642)	2,829
Investing activities			
Purchase of available-for-sale marketable securities	(91,657)	—	—
Purchases of property and equipment	(20)	(42)	(5)
Net cash used in investing activities	(91,677)	(42)	(5)
Financing activities			
Proceeds from convertible promissory notes	—	—	1,462
Financing costs on convertible promissory notes	—	—	(70)
Repayment of convertible promissory notes	—	—	(311)
Repayment of long-term debt	—	—	(307)
Proceeds from sale of common stock	—	100	—
Proceeds from sale of Junior A convertible preferred stock	—	—	7,642
Proceeds from the exercise of stock options	362	128	—
Proceeds from initial public offering, net of issuance costs	—	57,762	—
Proceeds from follow-on offering, net of issuance costs	75,231	—	—
Net cash provided by financing activities	75,593	57,990	8,416
Net cash increase (decrease) for the period	(37,562)	40,306	11,240
Cash and cash equivalents at beginning of period	52,663	12,357	1,117
Cash and cash equivalents at end of period	$ 15,101	$ 52,663	$12,357
Supplemental disclosure of cash flow information			
Cash paid for interest	$ —	$ —	$ 37
Noncash financing activities			
Conversion of convertible preferred stock to common stock	$ —	$ 65,586	$ —
Reclassification of prepaid IPO costs paid in 2013	—	1,465	—
Conversion of convertible promissory notes to Series D convertible preferred stock	—	—	3,888

See Notes to Financial Statements.

CARA THERAPEUTICS, INC.

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

1. Business

Cara Therapeutics, Inc. (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 pain and pruritus 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-based product candidates and raising capital.

As of December 31, 2015, the Company has raised aggregate net proceeds of approximately $204,800 from several rounds of equity financing, including its initial public offering, or IPO, which closed in February 2014 and its follow-on offering, which closed in August 2015 (see Note 12, *Stockholders' Equity*), and the issuance of debt. In addition, the Company earned approximately $32,500 under its license agreements for CR845, primarily with Maruishi Pharmaceutical Co. Ltd. ("Maruishi") and Chong Kun Dang Pharmaceutical Corp. ("CKD"), and for an earlier product candidate for which development efforts ceased in 2007.

In connection with the license of rights to CR845 in Japan to Maruishi and as part of the earnings described above, in April 2013, the Company received an upfront payment of $15,000, and in August 2014 and September 2015, the Company received an additional $480 and $1,725 (net of contractual foreign currency exchange adjustments), respectively, in milestone payments. In connection with the license of rights to CR845 in South Korea to CKD and as part of the earnings described above, in 2012, the Company received aggregate upfront and milestone payments of $1,190, and in August 2015 and October 2015, the Company received an additional $209 and $417 (net of South Korean withholding taxes), respectively, in milestone payments.

As of December 31, 2015, the Company had unrestricted cash and cash equivalents and marketable securities of $106,740 and an accumulated deficit of $104,891. 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 $24,690 and had net cash used in operating activities of $21,478 for the year ended December 31, 2015. The Company expects that cash and cash equivalents and marketable securities at December 31, 2015 will be sufficient to fund its operations beyond one year.

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 ("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 ("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 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.

CARA THERAPEUTICS, INC.

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

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 is 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, cash equivalents and marketable securities are held by a few 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.

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 section 320-10-20. The Company considers its marketable securities to be available-for-sale and, accordingly, these investments are recorded at fair value with unrealized gains and losses generally recorded in accumulated other comprehensive income (loss) ("AOCI") as a separate component of stockholders' equity. Marketable securities are reported in Marketable Securities in the Balance Sheets. Other income (expense), net, includes interest, realized gains and losses on sales of securities and other-than-temporary impairment ("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 ("OCI"), net of taxes. See Note 3, M*arketable Securities*, and Note 13, *Fair Value Measurement*.

CARA THERAPEUTICS, INC.

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

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 Accounting Standards Codification ("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, other 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. 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 pricing service. 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, 2015. The Company did not have any financial instruments categorized as level 2 as of December 31, 2014.

CARA THERAPEUTICS, INC.

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

Property and Equipment

Property and equipment (consisting of computer, office and laboratory equipment, furniture and fixtures, software 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
Furniture and fixtures	7 years
Software	3 years
Leasehold improvements	Lesser of 10 years or life of lease

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.

Common Stock and Convertible Preferred Stock Valuation

Due to the absence of an active market for the Company's common stock and convertible preferred stock prior to its IPO, the Company utilized methodologies in accordance with the framework of the American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation* (the "Practice Aid") to estimate the fair value of its common stock and convertible preferred stock at various reporting dates and in conjunction with various transactions. Each valuation included estimates and assumptions that required the Company's judgment. These estimates included assumptions regarding future performance, including the probability of successful completion of preclinical studies and clinical trials and FDA approval of product candidates containing CR845, and the probability and estimated time to complete financing and collaborative transactions. Significant changes to the key assumptions used in the valuations could have resulted in different fair values of common stock and convertible preferred stock at each valuation date. At the time of the completion of the Company's IPO on February 5, 2014, all convertible preferred stock was converted to its common stock. Subsequent to the IPO, the fair value of the Company's common stock is determined by reference to the relevant closing price of the Company's common stock on the NASDAQ Global Market.

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 research and development 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.

CARA THERAPEUTICS, INC.

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

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 stand-alone 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 determines the estimated selling price for deliverables within each agreement using vendor specific objective evidence ("VSOE") of selling price, if available, or third party evidence ("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. 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.

Arrangement consideration allocated to research and development 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 has determined that its research and developments services deliverables, as applicable, represent separate units of accounting because similar services are sold separately by other vendors.

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.

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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 ("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. Research and development expenses include, among other costs, salaries and other personnel-related costs, costs to conduct clinical trials, costs to manufacture product candidates and clinical supplies, laboratory supplies costs and facility-related costs. Non-refundable research and development 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, 2015 and 2014, the Company recorded $1,500 and $177 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, 2015 and December 31, 2014. 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* ("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,

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(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 lives), (iv) expected dividend yield on the Company's common stock, and (v) risk-free interest rates.

Prior to the effective date of the registration statement related to the Company's IPO in January 2014, the Company utilized methodologies in accordance with the Practice Aid to determine the fair value of the Company's common stock on any given date. Subsequently, the stock price input to the Black-Scholes model for each stock option granted is the closing price of the Company's common stock as quoted on The NASDAQ Global Market on the grant date.

Expected volatility is based on an analysis of guideline companies in accordance with ASC 718. The expected life 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, an accepted method for the Company's option grants under the SEC's Staff Accounting Bulletin No. 107, *Share-Based Payment.* 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 options' expected lives.

The Company applies a forfeiture rate to the number of unvested awards in each reporting period in order to accrue share-based compensation expense based on an estimate of the number of awards that are expected to vest. Estimated forfeiture rates are based upon historical data of awards that were cancelled prior to vesting. The Company adjusts the total amount of compensation cost recognized for each award, in the period in which each award vests, to reflect the actual forfeitures related to that award. To the extent that the actual forfeiture rate for an award is lower than the estimated forfeiture rate, additional compensation expense is recorded in the period that the award vests. Changes in the Company's estimated forfeiture rate will result in changes in the rate at which compensation cost for an award is recognized over its vesting period.

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 life of stock options granted to non-employees initially equal to the options' maximum contractual life of ten years, at issuance, and then revalues the 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. 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 converted or exercised during the period, when the effect is dilutive. Common stock equivalents may include convertible preferred stock, convertible promissory notes and outstanding stock options and stock warrants, which are included under the treasury stock method when dilutive. The computation of diluted net loss per share for each of the years ended December 31, 2015, 2014 and 2013 does not include common stock equivalents since such inclusion would be antidilutive.

During the year ended December 31, 2013, the Company computed basic net income (loss) per share available to common stockholders using the "two-class" method, which includes the weighted average number of shares of common stock outstanding during the period and other securities that participate in dividends (a participating security). Prior to its IPO, the Company's shares of convertible preferred stock were participating securities as defined by ASC 260-10, *Earnings Per Share*. In conjunction with the closing of the IPO on February 5, 2014, all outstanding shares of convertible preferred stock were automatically converted to shares of the Company's common stock (see Note 11, *Convertible Preferred Stock*).

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Under the two-class method, basic net income (loss) per share available to common stockholders is computed by dividing the net income (loss) available to common stockholders by the weighted average number of common shares outstanding for the period. The Company allocates net income on a pari passu (equal) basis to both common and preferred stockholders. Net losses are not allocated to preferred stockholders as they do not have an obligation to share in the Company's net losses. Diluted net income (loss) per share is computed using the more dilutive of (1) the two-class method, or (2) the "if-converted" method. Refer to Note 18, *Net Loss per Share*, for the Company's calculations of net loss per share available to common stockholders for the periods presented.

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 pain and pruritus.

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 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. Cash reimbursements received from landlords for leasehold improvements and other cash payments received from landlords as lease incentives 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.

Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update 2016-02, *Leases* ("ASU 2016-02"), which requires lessees to recognize a right-of-use asset and a lease liability on their balance sheets for all leases with terms greater than twelve months. Based on certain criteria, leases will be classified as either financing or operating, with classification affecting the pattern of expense recognition in the income statement. ASU 2016-02 is effective for periods beginning after December 15, 2018 and is required to be adopted using a modified retrospective approach for leases that exist or are entered into after the beginning of the earliest comparative period in the financial statements. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its financial statements.

In January 2016, the FASB issued Accounting Standards Update No. 2016-01, *Financial Instruments—Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities* ("ASU 2016-01"). The main objective of ASU 2016-01 is to enhance the reporting model for financial instruments to provide users of financial statements with more decision-useful information. The new guidance addresses certain aspects of recognition, measurement, presentation, and disclosure of financial instruments. ASU 2016-01 is effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years. The Company does not believe the adoption of this guidance will have a material impact on its financial statements.

In November 2015, the FASB issued Accounting Standards Update No. 2015-17, *Income Taxes (Topic 740) Balance Sheet Classification of Deferred Taxes* ("ASU 2015-17") as part of its simplification initiative to reduce complexity in accounting standards. ASU 2015-17 was issued because the current requirement that current and noncurrent portions of deferred taxes be presented separately on the balance sheet results in little or no benefit to

users of financial statements since the classification does not generally align with the time period in which the recognized deferred tax amounts are expected to be recovered or settled. ASU 2015-17 requires that deferred tax liabilities and assets be classified as noncurrent in a classified balance sheet. ASU 2015-17 is effective for financial statements issued for annual periods beginning after December 15, 2016, and interim periods within those annual periods. ASU 2015-17 may be applied either prospectively to all deferred tax liabilities and assets or retrospectively to all periods presented. If an entity applies the guidance prospectively, the entity should disclose in the first interim and first annual period of change, the nature of and reason for the change in accounting principle and a statement that prior periods were not retrospectively adjusted. If an entity applies the guidance retrospectively, the entity should disclose in the first interim and first annual period of change the nature of and reason for the change in accounting principle and quantitative information about the effects of the accounting change on prior periods. Earlier application of ASU 2015-17 is permitted for all entities as of the beginning of any interim or annual reporting period. The Company intends to adopt ASU 2015-17 prospectively as of January 1, 2017, which is not expected to have a material effect on its results of operations, financial position or cash flows.

During April 2015, the FASB issued Accounting Standards Update 2015-03 ("ASU 2015-03") *Interest—Imputation of Interest (Subtopic 835-30) Simplifying the Presentation of Debt Issuance Costs*, which simplifies the presentation of debt issuance costs by requiring debt issuance costs (e.g., legal fees, printing costs) to be presented as a deduction from the corresponding debt liability rather than as assets, as under current guidance. In August 2015, the FASB issued ASU 2015-15 *Interest—Imputation of Interest (Subtopic 835-30) Presentation and Subsequent Measurement of Debt Issuance Costs Associated with Line-of-Credit Arrangements* to clarify that, in the absence of authoritative guidance within ASU 2015-03 for debt issuance costs related to line-of-credit arrangements, the SEC staff would not object to an entity deferring and presenting debt issuance costs as an asset and subsequently amortizing the deferred debt issuance costs ratably over the term of the line-of-credit arrangement, regardless of whether there are any outstanding borrowings on the line-of-credit arrangement. ASU 2015-03 is effective for financial statements issued for periods beginning on January 1, 2016, including interim periods. Early adoption of ASU 2015-03 is permitted for financial statements that have not been previously issued. Upon adoption, the Company must apply the new guidance retrospectively to all prior periods presented in the financial statements. The Company does not expect the adoption of ASU 2015-03 or ASC 2015-15 to have a material effect on its financial position, results of operations or cash flows.

In August 2014, the FASB issued Accounting Standards Update 2014-15 *Presentation of Financial Statements – Going Concern (Subtopic 205-40), Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* ("ASU 2014-15"). ASU 2014-15 codifies, for the first time within GAAP, management's responsibility to evaluate whether there is substantial doubt about the Company's ability to continue as a going concern and to provide related footnote disclosures in connection with preparing financial statements for each annual and interim reporting period. Substantial doubt about the Company's ability to continue as a going concern exists when there are conditions or events, considered in the aggregate, that are known and reasonably knowable at the date that the financial statements are issued, that indicate that the Company will be unable to meet its obligations as they become due within one year after that date. ASU 2014-15 requires the Company to disclose the nature of those conditions or events when they are present, management's plans to mitigate those conditions or events and whether or not such plans alleviated the substantial doubt. ASU 2014-15 is effective for annual periods ending after December 15, 2016, and interim periods within annual periods beginning after December 15, 2016. Early application is permitted. Prior to adoption of ASU 2014-15, the Company evaluated the need to disclose its ability to continue as a going concern for a reasonable period of time based on projections of its ability to meet its obligations as they become due within a period of one year from the balance sheet date. Upon adoption of ASU 2014-15, that period will be extended to include one year from the date the financial statements are issued and the Company will be required to make the applicable disclosures in its financial statements. The Company does not expect that the adoption of ASU 2014-15 will have a material effect on its financial position, results of operations or cash flows.

In May 2014, the FASB issued Accounting Standards Update 2014-09, *Revenue from Contracts with Customers (Topic 606)* ("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

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consideration to which it expects to be entitled in exchange for the transfer of promised goods or services to customers. The amount of revenue to be recognized in any reporting period is determined by applying the following steps: (1) identify the contract(s) with a 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. ASU 2014-09 is effective for annual reporting periods beginning after December 15, 2017, including interim periods within that reporting period (i.e., January 1, 2018). The Company is allowed to adopt ASU 2014-09 either (1) retrospectively to each prior reporting period presented using several practical expedients related to completed contracts and required disclosures, or (2) using a modified retrospective approach, with the cumulative effect of initially applying ASU 2014-09 recognized as an adjustment to the opening balance of retained earnings of the annual reporting period that includes the date of initial application, including disclosure of the effect of using this method of adoption on the financial statement line items. The Company is currently in the process of deciding which method of adoption it will use and the effect of adoption of ASU 2014-09 on its results of operations, financial position and cash flows.

3. Available-for-Sale Marketable Securities

As of December 31, 2015, the Company's available-for-sale marketable securities consisted of money market mutual funds and debt securities issued by the U.S. government and government-sponsored entities and by investment grade institutions. As of December 31, 2014 and for the years ended December 31, 2014 and 2013, all of the Company's funds were held in money market savings and checking accounts that were classified as cash equivalents and not as available-for-sale marketable securities.

The following table summarizes the Company's available-for-sale marketable securities by major type of security as of December 31, 2015:

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market mutual funds	$ 42,017	$ —	$ (31)	$ 41,986
U.S. Treasury securities	2,528	—	—	2,528
Other U.S. government agency obligations	13,492	4	—	13,496
Corporate bonds	14,194	—	(6)	14,188
Commercial paper	19,444	1	(3)	19,442
Total available-for-sale marketable securities	$ 91,675	$ 5	$ (40)	$ 91,640

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

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The Company classifies its marketable debt securities based on their contractual maturity dates. The marketable debt securities as of December 31, 2015 mature at various dates through September 2016. The fair values and amortized cost 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,			
	2015		2014	
Contractual maturity	Fair Value	Amortized Cost	Fair Value	Amortized Cost
Less than one year	$ 49,653	$ 49,657	$ —	$ —

For the year ended December 31, 2015, there were no sales of available-for-sale marketable securities.

The following table shows 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, 2015	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses
Money market mutual funds	$ 30,985	$ (31)	$ —	$ —	$30,985	$ (31)
Corporate bonds	14,187	(6)	—	—	14,187	(6)
Commercial paper	11,960	(3)	—	—	11,960	(3)
Total	$ 57,132	$ (40)	$ —	$ —	$57,132	$ (40)

As of December 31, 2015, the Company held a total of 15 positions 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, 2015. The Company does not intend to sell these debt securities and the Company believes it is not more likely than not that it will be required to sell these securities before the recovery of their amortized cost basis, which may be maturity.

4. Accumulated Other Comprehensive Income (Loss)

The following table summarizes the changes in AOCI, net of tax, from unrealized gains (losses) on available-for-sale marketable securities, the Company's only component of AOCI, for the year ended December 31, 2015. As of December 31, 2014 and for the years ended December 31, 2014 and 2013, all of the Company's funds were held in money market savings and checking accounts that were classified as cash equivalents and not as available-for-sale marketable securities. For the year ended December 31, 2015, there were no reclassifications from AOCI since there were no sales of available-for-sale marketable securities.

	Total Accumulated Other Comprehensive (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)

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5. Prepaid Expenses

As of December 31, 2015, prepaid expenses was $1,729, consisting of $1,500 of prepaid R&D clinical costs, $98 of prepaid insurance, $96 of prepaid rent and $35 of other costs. As of December 31, 2014, prepaid expenses was $287, consisting of $92 of prepaid insurance, $177 of prepaid R&D clinical costs and $18 of other costs.

6. Property and Equipment, Net

Property and equipment, net consists of the following:

	December 31,	
	2015	2014
Computer and office equipment	$ 314	$ 309
Laboratory equipment	232	233
Furniture and fixtures	155	156
Software	126	126
Leasehold improvements	7,453	7,453
	$8,280	$8,276
Less accumulated depreciation and amortization	7,017	6,192
Property and equipment, net	$1,263	$2,084

Depreciation and amortization expense included in research and development expense and general and administrative expense was $839, $783 and $789 for the years ended December 31, 2015, 2014 and 2013, respectively.

In connection with the Company's relocation of its operating facility from Shelton, Connecticut to Stamford, Connecticut, the Company began accelerating the amortization of the Shelton leasehold improvements from December 2015 (see Note 21, *Commitments and Contingencies*).

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 21, *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. As of December 31, 2015, the restricted cash balance for the Shelton Lease was invested in a bank certificate of deposit and remains at $700 through the end of the lease term in 2017.

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For the Stamford Lease, the letter of credit balance remains at $769 for the first three years following commencement of the Stamford Lease and may, upon request from the Company, thereafter be reduced to $408 through the end of the lease term in 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, 2015, the money market account into which the Company will deposit the cash collateral for the letter of credit for the Stamford Lease had not been established and none of that cash was restricted. The restricted money market account was funded in January 2016. As of both December 31, 2015 and 2014, the Company had $700 of restricted cash in long-term assets.

8. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	December 31,	
	2015	2014
Accounts payable	$1,965	$ 515
Accrued research projects	1,542	549
Accrued professional fees	371	266
Accrued compensation and benefits	1,204	504
Accrued other	186	112
	$5,268	$1,946

9. Convertible Promissory Notes

In December 2012 and February 2013, the Company issued an aggregate of $4,000 principal amount of Convertible Promissory Notes ("Notes") due August 28, 2013 ("Maturity Date"). The sale was consummated through two closings. The initial closing was on December 28, 2012 for $2,538 principal amount. The final closing was on February 28, 2013 for $1,462 principal amount. All of the Notes were purchased by current stockholders, all of whom were given the opportunity to buy their pro rata share of the Notes. The holders of preferred stock who did not participate in the Note financing had their shares of preferred stock converted into common stock at their respective then applicable conversion rates. As a result, as of February 2013, 2,246,743 shares of preferred stock were converted into 959,545 shares of common stock.

Because the original terms of the preferred stock were modified to reflect this mandatory conversion, the Company determined that the preferred stock had been extinguished. Accordingly, the conversion date difference between the carrying value of the preferred stock converted ($4,466) and the fair value of the common stock issued ($3,575) has been recorded as a gain ($891) within accumulated deficit.

The Notes bore interest at 8% per annum and had a Maturity Date of August 28, 2013. The Notes were not eligible to be repaid prior to the maturity date without the consent of the holders of a majority in interest of the outstanding aggregate principal amount of the Notes. The Notes included an optional conversion feature and a mandatory conversion feature.

The optional conversion feature allowed the Note holder, any time prior to the Maturity Date, to elect to convert the balance of the note plus accrued interest into Series D convertible preferred stock at a conversion price of $1.444244 per share. In accordance with ASC 470-20, *Debt with Conversion and Other Options*, the Company determined that the intrinsic value of the beneficial conversion feature embedded in the Notes issued in the initial closing was $2,050, based on the estimated fair value of the Series D convertible preferred stock as of December 31, 2012 of $2.61 per share, and this intrinsic value was recorded as a debt discount, to be accreted to interest expense over the term of the Notes. As of December 31, 2012, the Company amortized $25 of debt discount to interest expense. As of February 28, 2013, the final closing of the Note financing, the Company determined that the intrinsic

value of the beneficial conversion feature of the Notes issued in the final closing was $1,382 and recorded this amount as an additional debt discount. For the year ended December 31, 2013, the Company amortized $3,407 of debt discount to interest expense.

The mandatory conversion of the Notes would have occurred in the event the Company issued or sold equity securities on or before August 28, 2013 of not less than $10,000. In this event, the Notes plus all accrued interest would have automatically converted into the issued class of equity securities at a price per share equal to 90% of the cash price paid by the investors in the new equity securities. In accordance with ASC 815-15, *Derivatives and Hedging*, the Company was required to record the embedded mandatory conversion feature as a free-standing financial instrument, as the conversion feature was a substantial contingent call option. The Company recorded $41 as the fair value of the contingent call option liability related to the Notes issued in the initial closing of the Note financing as of December 31, 2012, with a corresponding amount recorded as additional debt discount, with the debt discount to be accreted to interest expense over the life of the Notes. Any increases or decreases to the fair value of the contingent call option would be recorded in operations through the life of the Notes.

The Company estimated the fair value of the contingent call option by estimating the accreted value of the Notes upon conversion, with consideration provided for the 10% price discount and the probability of the Company closing an equity offering in excess of $10,000 before August 28, 2013. The Company classified the liability within Level 3 of the fair value hierarchy as the probability factor is an unobservable input and significant to the valuation model. Increases in the probability of an equity offering closing before August 28, 2013 in excess of $10,000 would increase the fair value of the liability. In April 2013, the estimated fair value of the contingent call option of $41 was reduced to zero with an equal reduction in interest expense, since the Company estimated the probability of closing a $10,000 equity offering before August 28, 2013 as zero, following the receipt of $23,000 in connection with the Maruishi transaction in April 2013, which removed the need for a $10,000 financing prior to August 28, 2013.

Prior to the Maturity Date, the Company received notice from Note holders to convert Notes in the aggregate amount of $3,888 in principal plus accrued interest, into 2,692,291 shares of Series D convertible preferred stock, and the remaining Notes, in the aggregate amount of $311 in principal and accrued interest, were repaid during October 2013.

Deferred financing costs related to the convertible promissory notes were amortized over the life of the related debt using the effective interest method. For the year ended December 31, 2013, deferred financing cost of $117 was amortized and included in interest expense, within other income (expense), net.

10. Long-Term Debt

In September 2007, the Company entered into a $4,000 term loan ("Loan") with Connecticut Innovations Inc. ("CII"). The Loan carried a 7% interest rate and was payable in monthly installments over five years. The Loan was collateralized by property and equipment which was owned by the Company that was located in Shelton, Connecticut. The CII Loan contained certain non-financial covenants, including the requirement that the Company maintain its principal place of business and conduct the majority of its operations in Connecticut. If the Company failed to maintain its Connecticut presence, all amounts due under the Loan would be immediately due and payable with the cumulative interest rate increasing to 25%.

On September 4, 2012, the Company and CII amended the Loan to defer all payments due between July 1, 2012 and December 31, 2012 until January 2, 2013 and to increase the interest rate to 8.5%. The Company repaid the remaining principal balance of $307 plus accrued interest outstanding under the Loan in April 2013.

In connection with the Loan, the Company issued to CII a warrant to purchase 19,851 shares of common stock at an exercise price of $10.08. The fair value of such warrant at the date of issuance was determined not to be material. The warrant also incorporated the non-financial covenants of the Loan described above. If the Company failed to maintain its Connecticut presence, it would be required to pay CII the excess of the market price of the common stock over the warrant exercise price for all unexercised shares represented by the warrant and/or the exercise price paid plus the market price on any shares acquired through a previous exercise of the warrants. On July 31, 2014, CII exercised its outstanding warrant in a cashless exercise, resulting in the issuance of 6,383 shares of the Company's common stock.

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11. Convertible Preferred Stock

In connection with the Notes (refer to Note 9, *Convertible Promissory Notes*), as of February 2013, the holders of 2,246,743 shares of preferred stock who did not participate in the Note financing had their shares of preferred stock converted into 959,545 shares of common stock.

In April 2013, the Company issued to Maruishi (refer to Note, 14, *Collaborations*) 2,105,263 shares of Junior A convertible preferred stock ("Junior A Preferred Stock"), having an estimated fair value of $7,663. The shares were sold as part of the license transaction with Maruishi.

In September 2013, the Company issued an aggregate of 2,692,291 shares of Series D convertible preferred stock upon the conversion of the Notes (refer to Note 9, *Convertible Promissory Notes*). Each series of convertible preferred stock is referred to as that series' Preferred Stock. All series of convertible stock are, collectively, referred to as Preferred Stock.

The following tables summarize the outstanding Preferred Stock as of December 31, 2013 and December 31, 2012:

As of December 31, 2013

	Preferred Shares Authorized	Preferred Shares Issued and Outstanding	Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Junior	173,611	173,611	$ 500	$ 354	69,444
Junior A	2,105,263	2,105,263	8,000	7,642	842,105
Series A	1,677,118	1,677,118	1,677	1,677	670,830
Series B	2,254,417	2,254,417	4,509	4,509	980,163
Series C	10,930,946	10,930,946	33,886	33,886	5,173,413
Series D	12,260,845	12,045,574	17,397	17,518	4,818,216
	29,402,200	29,186,929	$ 65,969	$65,586	12,554,171

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As of December 31, 2012

	Preferred Shares Authorized	Preferred Shares Issued and Outstanding	Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Junior	173,611	173,611	$ 500	$ 354	69,444
Junior A	—	—	—	—	—
Series A	2,000,000	2,000,000	2,000	2,000	800,000
Series B	2,370,000	2,370,000	4,740	4,740	1,030,434
Series C	11,706,450	11,706,450	36,290	36,290	5,540,457
Series D	10,386,057	10,386,057	15,000	15,138	4,154,422
	26,636,118	26,636,118	$ 58,530	$58,522	11,594,757

Upon the closing of the Company's IPO on February 5, 2014, all 29,186,929 shares of the Company's Preferred Stock that were issued and outstanding on that date were automatically converted into an aggregate of 12,554,171 shares of its common stock. As of December 31, 2015 and 2014, there were no shares of Preferred Stock issued or outstanding.

Prior to automatic conversion of the Preferred Stock to common stock upon the closing of the Company's IPO, the following terms and conditions applied to the Preferred Stock:

Liquidation Preferences

In the event of any voluntary or involuntary liquidation, dissolution, or winding up of the Company, including a deemed liquidation event, as defined in the Company's amended and restated certificate of incorporation, the following liquidation preferences as of December 31, 2013 were payable to the holders of Preferred Stock: Series D Preferred Stock, aggregate liquidation preference of $17,397, plus declared, but unpaid dividends; Series C Preferred Stock, aggregate liquidation preference of $33,886, plus declared, but unpaid dividends; Series B Preferred Stock, aggregate liquidation preference of $4,509, plus declared, but unpaid dividends; Series A Preferred Stock, aggregate liquidation preference of $1,677 plus declared, but unpaid dividends; Junior A Preferred Stock, aggregate liquidation preference of $8,000 plus declared, but unpaid dividends; and Junior Preferred Stock, aggregate liquidation preference of $500 plus declared, but unpaid dividends. The Series D Preferred Stock liquidation preferences are senior to Series C Preferred Stock liquidation preferences, the Series C Preferred Stock liquidation preferences are senior to the Series B Preferred Stock liquidation preferences, the Series B Preferred Stock liquidation preferences are senior to the Series A Preferred Stock liquidation preferences, the Series A Preferred Stock liquidation preferences are senior to the Junior A Preferred Stock liquidation preferences, and the Junior A Preferred Stock liquidation preferences are senior to the Junior Preferred Stock liquidation preferences. If all amounts would have been paid to the holders of the Preferred Stock in respect of their liquidation preferences, then the remaining assets of the Company would have been distributed pro rata to the holders of Series D Preferred Stock and the common stockholders, subject to a maximum of an additional $4.332732 per share for the holders of Series D Preferred Stock. As a result, the Series D Preferred Stock's total liquidation preference could have been up to $70,000, exclusive of any declared, but unpaid dividends.

The amount that each holder of Preferred Stock would have received upon liquidation, dissolution or winding up of the Company would have been the greater of the cumulative amounts described above or the amount that such holder of Preferred Stock would have received if the shares of Preferred Stock converted into common stock immediately prior to the liquidation, dissolution or winding up of the Company.

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Conversion

Each holder of Preferred Stock had the right to convert any or all of such holder's Preferred Stock into common stock at any time. As of December 31, 2013, Junior Preferred Stock, Junior A Preferred Stock, Series A Preferred Stock and Series D Preferred Stock were convertible into common stock at a conversion ratio of one to 0.4 and Series B and Series C were convertible into common stock at a conversion ratio of one to 0.434782 and one to 0.473282, respectively. The conversion ratio for all Preferred Stock was subject to adjustment based on certain events specified in the Company's amended and restated certificate of incorporation, including a stock split, if the Company pays a dividend to common stockholders without a corresponding dividend to the Preferred Stockholders or if the Company sells, or is deemed to sell, common stock at a price per share that is less than the then effective conversion prices of each class of Preferred Stock. Pursuant to these provisions, the conversion ratio for the Series B Preferred Stock and Series C Preferred Stock was adjusted upon the issuance of the Series D Preferred Stock.

Automatic Conversion

Contemporaneously with the closing of a qualified public offering of common stock, as defined in the Company's amended and restated certificate of incorporation, or upon a vote of the holders of a majority of the Preferred Stock, voting together as a single class, and holders of at least 67% of the Series D Preferred Stock, all outstanding shares of Preferred Stock would automatically convert into common stock at the then effective applicable conversion rates for such shares. Contemporaneously with the closing of the Company's IPO, all outstanding shares of Preferred Stock were automatically converted into common stock at the then effective applicable conversion rates for such shares (see above).

Dividends

Dividends on all series of outstanding Preferred Stock were payable when and if declared by the Company's Board of Directors. No dividends shall be paid to the holders of the Company's common stock unless equivalent dividends have been declared and paid on each series of outstanding Preferred Stock. No dividends were declared or paid by the Company for any period during which the Preferred Stock was outstanding through the date of the closing of the Company's IPO.

Voting Rights

As set forth in the Company's amended and restated certificate of incorporation, the holders of Series A, Series B, Series C and Series D Preferred Stock ("Senior Preferred Stock") were entitled to vote as one class, with common stockholders, based on the number of shares of common stock each holder would receive upon conversion of their Senior Preferred Stock into shares of common stock, for all matters except for the approval of certain major actions by the Company and the election of directors. Subject to certain ownership thresholds and certain nomination and approval rights set forth in the Company's amended and restated certificate of incorporation and an amended and restated voting agreement by and among the Company and certain stockholders of the Company, directors are elected as follows: common stockholders vote as a separate class for the election of two directors; the holders of Series D Preferred Stock vote as a separate class for the election of one director; the holders of Series C Preferred Stock vote as a separate class for the election of three directors; and the holders of Senior Preferred Stock vote as a combined class for the election of one director. Upon the closing of the Company's initial public offering on February 5, 2014, the voting agreement terminated and the Company's stockholders no longer have any special rights regarding the election or designation of members of its Board of Directors.

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Registration Rights

The former holders of shares of Preferred Stock have certain registration rights as set forth in an amended and restated investors' rights agreement by and among the Company and certain of its stockholders.

12. 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, 2015, there were 27,254,863 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 January 30, 2014, the Company's registration statement on Form S-1 relating to its IPO was declared effective, providing for the sale of 5,750,000 shares of the Company's common stock at a public offering price of $11.00 per share, for an aggregate offering price of $63,250. As a result of the IPO, the Company received net proceeds of $56,297 after deducting $6,953 of underwriting discounts and commissions and offering expenses paid by the Company.

On December 1, 2014, the Company sold 11,442 shares of common stock to its Chief Medical Officer at $8.74 per share (which was the closing price of the Company's common stock on the NASDAQ Global Market on that date) for gross proceeds of $100. The shares of common stock have not been registered under the Securities Act of 1933, as amended (the "Securities Act"), and have been sold pursuant to an exemption from registration contained in the Securities Act based in part upon the purchaser's representations contained in the purchase agreement.

On July 29, 2015, the Company entered into an underwriting agreement (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 (the "Offering"). The 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 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 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.

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13. Fair Value Measurements

The following table summarizes the Company's financial assets measured at fair value on a recurring basis as of December 31, 2015 and 2014 and by level within the fair value hierarchy:

Fair value measurement as of December 31, 2015:

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 mutual funds, savings account and checking account	$ 15,101	$ 15,101	$ —	$ —
Available-for-sale marketable securities:				
Money market mutual funds	41,986		41,986	—
U.S. Treasury securities	2,528		2,528	—
Other U.S. government agency obligations	13,496		13,496	—
Corporate bonds	14,188		14,188	—
Commercial paper	19,442		19,442	—
Restricted cash:				
Bank Certificate of Deposit	700	700	—	—
Total financial assets	$107,441	$ 15,801	$ 91,640	$ —

Fair value measurement as of December 31, 2014:

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 equivalents:				
Money market savings account and checking account	$ 52,663	$ 52,663	$ —	$ —
Restricted cash:				
Bank Certificate of Deposit	700	700	—	—
	$ 53,363	$ 53,363	$ —	$ —

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, 2015, 2014 and 2013. There were no transfers of financial assets between Levels 1, 2, or 3 classifications during the years ended December 31, 2015, 2014 and 2013.

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14. Collaborations

Chong Kun Dang Pharmaceutical Corporation

In April, 2012, the Company entered into a license agreement with CKD (the "CKD Agreement") that provides CKD with the exclusive rights to develop, manufacture and commercialize products containing CR845 in South Korea. Under the CKD 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. The Company has accounted for the milestones under ASC 605 *Revenue Recognition – Milestone Method*. At the time of execution of the CKD 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.

In exchange for the $1,000, the Company provided CKD with the license for CR845 and issued CKD 173,611 shares of Junior Preferred Stock. The Company recorded the issuance of the 173,611 shares of Junior Preferred Stock as a capital transaction for $354, which represented the shares' estimated fair value as of the transaction date. The remaining proceeds of $646 were recorded as license revenue as the license was the only deliverable within the agreement that had stand-alone value and was determined to be a separate unit of accounting under ASC 605-25, *Revenue Recognition Multiple – Element Arrangements*.

In July 2015, the Company met the milestone criteria, as set forth in the CKD Agreement, for completion of a Phase 1b trial of Oral CR845 in the United States. As a result, in August 2015, the Company received a milestone payment of $209 (net of South Korean withholding tax of $41) from CKD. In September 2015, the Company met the milestone criteria, as set forth in the CKD Agreement, for completion of a Phase 2 trial of CR845 in uremic pruritus patients in the United States. As a result, in October 2015, the Company received a milestone payment of $417 (net of South Korean withholding tax of $83) from CKD. Both milestones were considered to be substantive and the full amount of the milestone payments was recognized as milestone revenue when the milestones were achieved.

The next potential milestone that the Company could be entitled to receive under the CKD Agreement will be a clinical development milestone for completion of a Phase 3 trial of CR845 in uremic pruritus in the United States. 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 (the "Maruishi Agreement") under which the Company granted Maruishi an exclusive license to develop, manufacture, and commercialize drug products containing CR845 for acute pain and uremic pruritus in Japan. 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 in the United States and Japan, respectively. In addition, the Company provided Maruishi specific clinical development services for CR845 used in Maruishi's field of use.

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 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 at the outset of the arrangement.

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As a result, the total value of the arrangement of $15,337 (consisting of the $15,000 upfront payment, plus the additional amount assigned to these deliverables as a result of the Junior A Preferred Stock premium, see below) was allocated between the two units of accounting. 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 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 this license agreement, the management of the Company determined that the license and the R&D services had estimated selling prices of $10,200 and $6,200, respectively. The resulting percentage allocations were applied to the $15,337 of total consideration, which resulted in $9,637 being assigned to the license unit of accounting, which was recognized immediately as license revenue, while $5,700 was assigned to the R&D services unit of accounting. 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. As of December 31, 2015 and 2014, the Company had $0 and $1,452, respectively, of deferred revenue pursuant to the R&D services deliverable under the Maruishi Agreement.

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 in acute post-operative pain, which constituted achievement of one of the milestones specified in the license 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, 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 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 milestone revenue and $641 as collaborative revenue in connection with achievement of this milestone.

The next potential milestone that the Company could be entitled to receive under the Maruishi Agreement will be a clinical development milestone for the completion of the first Phase 3 pivotal trial of CR845 in acute pain in the United States. If achieved, this milestone will result in a payment of $1,000, before contractual foreign currency exchange adjustments, being due to the Company.

Along with the R&D services performed by the Company for Maruishi, the Company supplied Maruishi with CR845 clinical material as an accommodation. The Company had previously entered into manufacturing and service

agreements with third parties to manufacture CR845. Payments made by the Company to third parties based on firm and fixed commitments by Maruishi to purchase CR845 from the Company were capitalized as prepaid expense. During the manufacturing process, title and risk of loss remained with the third party until the Company paid in full for the material.

Once the Company had title to the CR845 and had delivered it to Maruishi, prepaid expense related to that CR845 was reduced with an offset to R&D expense. At that time, Maruishi reimbursed the Company for its external and internal costs for purchasing CR845 and processing the sale to Maruishi and the Company recognized clinical compound revenue for the reimbursement amount. During the years ended December 31, 2015, 2014 and 2013, the Company recognized clinical compound revenue of $0, $674 and $102, respectively. Deposits received from Maruishi prior to delivery of CR845 were recorded as deferred revenue.

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 sublicense fees (subject to certain credits for milestone payments already made) if Maruishi enters into a sublicense agreement regarding the product candidates.

Also, in conjunction with entering into this arrangement, Maruishi purchased 2,105,263 shares of Junior A Preferred Stock of the Company pursuant to a stock purchase agreement for a purchase price of $3.80 per share, for total consideration of $8,000. These shares have been recorded at their fair value of $7,663 or $3.64 per share. As a result, the premium of $337 was allocated to the arrangement consideration (see above).

The Company incurred R&D expense related to the Maruishi Agreement of $1,583 (consisting of clinical trial costs related to the R&D services deliverable), $3,558 (consisting of $3,000 of clinical trial costs related to the R&D services deliverable and $558 related to cost of clinical compound sold to Maruishi) and $2,452 (consisting of $2,420 of clinical trial costs related to the R&D services deliverable and $32 related to cost of clinical compound sold to Maruishi) during years ended December 31, 2015, 2014 and 2013, respectively.

15. Stock-Based Compensation

2014 Equity Incentive Plan

The Company's 2014 Equity Incentive Plan, or 2014 Plan, is administered by the Company's Board of Directors or a duly authorized committee thereof (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, "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 non-employee 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, which, to date, has been 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months. The Plan Administrator determines the term of Stock Awards granted under the 2014 Plan up to a maximum of ten years.

Initially, the aggregate number of shares of the Company's common stock that may be issued pursuant to Stock Awards under the 2014 Plan was 1,600,000 shares. Additionally, the number of shares of the Company's common stock reserved for issuance under the 2014 Plan will automatically increase on January 1 of each year, beginning on January 1, 2015 and continuing through and including January 1, 2024, by 3% of the total number of shares of 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. The maximum number of shares that may be issued pursuant to the

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exercise of incentive stock options under the 2014 Plan is 30,000,000 shares. On January 1, 2015 and January 1, 2016, the aggregate number of shares of common stock that may be issued pursuant to stock awards under the Company's 2014 Equity Incentive Plan automatically increased to 2,284,061 and 3,101,707, respectively.

2004 Stock Incentive Plan

The Company's 2004 Stock Incentive Plan (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 has 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 December 31, 2015 and changes during the year then ended is as follows:

	Number of Options	Weighted-Average Exercise Price	Aggregate Intrinsic Value
Outstanding at December 31, 2014	1,022,360	$ 8.16	
Granted	774,000	11.77	
Exercised	(124,868)	2.89	
Expired	(8,000)	0.25	
Forfeited	(5,084)	10.45	
Outstanding at December 31, 2015	1,658,408	$ 10.27	$ 11,058
Weighted average remaining contractual life as of December 31, 2015 (yrs)	8.31		
	510,298	$ 7.78	$ 4,634
Weighted average remaining contractual life as of December 31, 2015 (yrs)	6.59		
Options vested and expected to vest at December 31, 2015	1,574,746	$ 10.14	$ 10,693
Weighted average remaining contractual life as of December 31, 2015 (yrs)	8.26		

The total fair value of options vested during the years ended December 31, 2015, 2014 and 2013 was $2,489, $393 and $75, respectively. The intrinsic value of options exercised during the years ended December 31, 2015, 2014 and 2013 was $1,748, $2,055 and $0, respectively.

During the years ended December 31, 2015 and 2014, the Company granted 774,000 and 884,000 stock options, respectively, to employees, non-employee members of the Board of Directors or non-employee consultants.

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The Company did not grant any stock options during the year ended December 31, 2013. 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,	
	2015	2014
Risk-free interest rate	1.43% - 1.89%	1.64% - 2.72%
Expected volatility	64.0% - 67.4%	64.9% - 71.3%
Expected dividend yield	0%	0%
Expected life of employee and Board of Directors' options (in years)	6.25	6.25
Expected life of non-employee options (in years)	10	10

The weighted average grant date fair value of options granted to employees, non-employee members of the Board of Directors for their Board service and non-employee consultants during the years ended December 31, 2015 and 2014 was $7.17 and $7.09, respectively.

At the end of each fiscal quarter during the years ended December 31, 2015, 2014 and 2013, the Company used the Black-Scholes option valuation model with the following ranges of assumptions to re-measure the fair value of all outstanding unvested options that had been granted to non-employee consultants until each option grant was fully vested.

	Year Ended December 31,		
	2015	2014	2013
Risk-free interest rate	1.81% - 2.15%	1.96% - 2.72%	2.5% - 3.2%
Expected volatility	70.6% - 72.2%	69% - 71%	71% - 72%
Expected dividend yield	0%	0%	0%
Expected life of non-employee options (in years)	8.1 - 8.8	6 - 10	1.5 – 7

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

The weighted average fair values of outstanding unvested options that had been granted to non-employee consultants as re-measured during the years ended December 31, 2015, 2014 and 2013 were $10.05, $10.77 and $6.54, respectively.

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During the years ended December 31, 2015, 2014 and 2013, the Company recognized compensation expense in the accompanying Statements of Comprehensive Loss relating to stock options, as follows:

	Year Ended December 31,		
	2015	2014	2013
Research and development	$1,073	$ 349	$ 71
General and administrative	1,441	1,022	52
Total stock option expense	$2,514	$1,371	$123

As of December 31, 2015, 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 $7,036, which is expected to be realized over a weighted average period of 2.98 years. The Company will issue shares upon exercise of options from common stock reserved.

16. Income Taxes

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

	December 31,		
	2015	2014	2013
Current:			
Federal	$ —	$ —	$ —
State	(397)	(201)	(30)
	(397)	(201)	(30)
Deferred:			
Federal	—	—	—
State	—	—	—
	—	—	—
Benefit from income taxes	$ (397)	$ (201)	$ (30)

The Company's tax benefits relate to state research and development tax credits exchanged for cash. The State of Connecticut provides companies with the opportunity to exchange certain research and development credit carryforwards for cash in exchange for foregoing the carryforward of the research and development credit. The program provides for such exchange of the research and development credits at a rate of 65% of the annual research and development credit, as defined.

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A reconciliation of income taxes computed using the U.S. federal statutory rate to that reflected in operations is as follows:

	December 31,		
	2015	2014	2013
Income taxes using U.S. federal statutory rate	34.00%	34.00%	34.00%
State income taxes, net of federal benefit	5.95%	5.23%	6.03%
Impact of R&D tax credit on effective tax rate	3.14%	3.03%	12.04%
Stock option shortfalls and cancellations	-0.03%	-0.69%	0.00%
Permanent items and other	-0.41%	-0.57%	-1.42%
Change in valuation allowance	-41.07%	-39.88%	-49.90%
	1.58%	1.12%	0.75%

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

	December 31,	
	2015	2014
Net operating loss carryforwards	$ 36,217	$ 27,094
Federal and state tax credits	4,315	3,508
Accelerated depreciation	1,206	1,018
Deferred revenue	—	566
Stock-based compensation expense	1,106	333
Other	189	197
	43,033	32,716
Valuation allowance	(43,033)	(32,716)
Net deferred tax asset	$ —	$ —

A 100% valuation allowance has been recorded on the deferred tax asset as of December 31, 2015 and 2014 because management believes it is more likely than not that the asset will not be realized. The change in the valuation allowance during 2015 and 2014 was $10,317 and $7,156, respectively.

The Company has a tax benefit of approximately $839 related to the exercise of non-qualified stock options and the disqualified disposition of incentive stock options. Pursuant to ASC 718, the benefit will be recognized and recorded to additional paid-in-capital when the benefit is realized through the reduction of taxes payable.

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, 2015 and 2014, 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.

As of December 31, 2015, the Company's U.S. federal tax return for 2014 is under examination by the Internal Revenue Service.

At December 31, 2015, the Company had federal and state net operating loss carryforwards of approximately $95,900 and $89,899, 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 382. The Company also had federal and state research and development tax credit carryforwards of approximately $3,642 and $707, 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 2007 through 2015 remain open to U.S. federal and state tax examinations.

17. License and Research Agreement

Effective April 2005, the Company entered into a semi-exclusive worldwide royalty-free license agreement (the "Glasgow License Agreement") for a certain G protein-coupled receptor ("GPCR") assay technology with the University of Glasgow ("Glasgow"). The Company issued 200,000 shares of its common stock to Glasgow as compensation for this license.

Upon an exit event, including an IPO or as otherwise defined in the Glasgow License Agreement, Glasgow had the option to require the Company to guarantee a return of $1,000 on its 200,000 shares of common stock. If the proceeds from the exit event resulted in a return of less than $1,000, the Company was required to make an additional license payment by giving Glasgow cash or through the issuance of additional shares (at the Company's option), as specified in the Glasgow License Agreement. In accordance with ASC 480, *Distinguishing Liabilities from Equity*, the Company initially recorded the fair value of this option as both a long-term liability and research and development expense. The Company estimated the fair value of the option using the Black-Scholes option valuation model with consideration given to the probability of an exit event occurring below the guaranteed amount. The fair value of the liability was estimated at each subsequent balance sheet date, with any increases or decreases to the fair value recorded as increases or decreases to research and development expense and the related liability. As of December 31, 2013, the estimated fair value of the liability was reduced to zero based on the Company's estimated fair value of common stock after the Maruishi transaction (see Note 11, *Collaborations*). The Company classified the liability within Level 3 as the probability factor is an unobservable input and significant to the valuation model. The Company used a probability factor of 10% in all periods from 2005 to 2013. The probability rate was based on the successful progress of the Company's product candidates containing CR845 and the Company's expectation of an exit event value below the guaranteed amount. An increase in the probability rate would have resulted in a higher liability while an increase in the stock price would have reduced the liability. The decrease in the value of the liability of $35 in 2013 was the result of changes in the observable inputs (i.e. stock value, interest rates and volatility) and was recorded in research and development expense. The closing of the Company's IPO on February 5, 2014 constituted an exit event under the Glasgow License Agreement. Since the public offering price in the IPO was $11.00 per share, the aggregate exit event value was greater than the guaranteed amount. Consequently, as of December 31, 2014, the Company no longer had a liability under the Glasgow License Agreement.

18. Net Loss per Share

The Company computes net loss per share available to common stockholders in accordance with ASC 260-10, *Earnings per Share* (see Note 2, *Significant Accounting Policies – Income (Loss) per Share*).

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The denominators used in the net loss per share available to common stockholders computations are as follows:

	Year Ended December 31,		
	2015	2014	2013
Basic:			
Weighted average shares outstanding	24,620,372	20,965,935	4,133,138
Diluted:			
Weighted average shares outstanding - Basic	24,620,372	20,965,935	4,133,138
Convertible preferred stock*	—	—	—
Common stock options*	—	—	—
Common stock warrants*	—	—	—
Convertible promissory notes (as converted)*	—	—	—
Demoninator for diluted net loss per share available to common stockholders	24,620,372	20,965,935	4,133,138

* No amounts were considered as their effects would be anti-dilutive.

Basic and diluted net loss per share available to common stockholders are computed as follows:

	Year Ended December 31,		
	2015	2014	2013
Net loss	$ (24,690)	$ (17,745)	$ (3,963)
Add back: extinguishment of preferred shares	—	—	891
Net loss available to common stockholders - Basic and Diluted	$ (24,690)	$ (17,745)	$ (3,072)
Weighted-average common shares outstanding available to common stockholders			
Basic and Diluted	24,620,372	20,965,935	4,133,138
Net loss per share available to common stockholders:			
Basic and Diluted	$ (1.00)	$ (0.85)	$ (0.74)

Securities outstanding at the end of the respective periods presented below, that could potentially dilute basic earnings per share in the future, that were not included in the computation of diluted net loss per share because to do so would have been antidilutive are as follows:

	Year Ended December 31,		
	2015	2014	2013
Convertible preferred stock	—	—	12,554,171
Common stock options	1,658,408	1,022,360	490,160
Common stock warrants	—	—	19,851

All shares of the Company's convertible preferred stock were automatically converted to shares of the Company's common stock upon the closing of the IPO on February 5, 2014 (see Note 11, *Convertible Preferred Stock*). All common stock warrants were exercised in a cashless exercise on July 31, 2014 (see Note 10, *Long-Term Debt*).

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19. Related Party Transactions

The Company is party to a consulting agreement with a founder and a common stockholder of the Company who provides scientific advisory services. Total expenses under this agreement were $164, $169 and $134 for the years ended December 31, 2015, 2014 and 2013, respectively. Included in accounts payable and accrued expenses as of December 31, 2015 and 2014, respectively, was $21 and $35 for amounts due to this stockholder.

20. 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 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. The plan allows the Company to match employee contributions; however, there were no matching contributions paid through December 31, 2014. 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 year ended December 31, 2015, employer contributions to the plan were $80.

21. Commitments and Contingencies

Shelton Operating Lease

As of December 31, 2015, the Company leases its operating facility located in Shelton, Connecticut. The lease agreement, as amended, requires monthly lease payments through October 13, 2017. At inception of the lease, the Company received an incentive allowance from the landlord of $2,127. The Company recorded the incentive allowance as leasehold improvements and deferred lease obligation. The Company is recording monthly rent expense associated with the lease on a straight-line basis over the ten-year minimum term of the lease reduced by the amortization of the deferred lease obligation over the same time period. As a result of this straight-line basis, deferred lease obligation includes $374 and $582 of unamortized incentive allowance plus $211 and $292 of accrued rent at December 31, 2015 and 2014, respectively.

Total rent expense under the operating lease was $665, $643 and $616 for the years ended December 31, 2015, 2014 and 2013, respectively.

Future minimum rental payments under the Shelton operating lease at December 31, 2015 are as follows:

2016	$ 913
2017	740
Total	$1,653

In conjunction with the signing of the Shelton, Connecticut lease, the Company entered into a standby letter of credit agreement for $2,170, which expires on May 31, 2017 as a security deposit for the premises. In accordance with the terms of the lease, because no drawing was made against the standby letter of credit nor has any default under the operating lease occurred, the amount of the letter of credit was automatically reduced by $294 annually starting March 1, 2008 until the stated amount reached a balance of $700, which occurred in 2012. This standby letter of credit is secured with restricted cash (refer to Note 7, *Restricted Cash*).

In connection with the relocation of the Company's operating facility from Shelton to Stamford, Connecticut (see below), as of December 31, 2015, the Company was negotiating with the Shelton landlord regarding the Company's future obligations under the Shelton lease.

The Company is accelerating the amortization of the Shelton leasehold improvements from the date of signing of the Stamford lease through the expected date that the Company will vacate the Shelton facility. Additional amortization expense as a result of such acceleration amounted to $67 during the year ended December 31, 2015 and will be $899 for the period from January through May 2016.

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Stamford Operating Lease

In December 2015, the Company entered into a lease agreement (the "Stamford Lease") with Four Stamford Plaza Owner LLC (the "Landlord") for office space in Stamford, Connecticut (the "Premises"). The purpose of the Stamford Lease is to relocate the Company's corporate headquarters. The Stamford Lease commences upon completion of renovations to the Premises, which is expected to be in May 2016 (the "Commencement Date"), and ends 90 months thereafter. The Stamford Lease requires monthly lease payments, including rent escalations and rent holidays, during the initial lease term. The Company will begin to make rental payments from the Commencement Date. The Stamford Lease is renewable for one five-year term.

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 expires on December 16, 2016 and is automatically renewed annually through November 1, 2023. This standby letter of credit will be secured with restricted cash in a money market account, although the restricted money market account was not established until January 2016 (refer to Note 7, *Restricted Cash*).

Future minimum rental payments under the Stamford Lease at December 31, 2015 are as follows:

2016	$ 288
2017	875
2018	1,093
2019	1,217
2020	1,241
Thereafter	3,650
Total	$ 8,364

Under the Stamford Lease, the Landlord will contribute approximately $1,021 toward the cost of tenant improvements to the Premises as an incentive allowance. At the Commencement Date, the Company will record the incentive allowance as a leasehold improvements asset and a deferred lease obligation liability. The Company will record monthly rent expense associated with the Stamford Lease on a straight-line basis from the Commencement Date through the 7.5-year minimum term of the Stamford Lease, reduced by the amortization of the deferred lease obligation over the same time period.

22. 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.

23. Quarterly Results of Operations (Unaudited)

The following tables contain selected financial data for each quarter of the years ended December 31, 2015 and 2014. 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, 2015 and 2014. The operating results for any period are not necessarily indicative of results for any future periods.

CARA THERAPEUTICS, INC.

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	Year Ended December 31, 2015			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$ 489	$ 874	$ 2,440	$ —
Net loss - Basic and Diluted	(4,689)	(5,684)	(4,787)	(9,530)
Loss per share - Basic and Diluted	$ (0.21)	$ (0.25)	$ (0.19)	$ (0.35)

	Year Ended December 31, 2014			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$ 178	$ 960	$ 1,125	$ 914
Net loss - Basic and Diluted	(3,383)	(3,645)	(6,545)	(4,172)
Loss per share - Basic and Diluted	$ (0.22)	$ (0.16)	$ (0.29)	$ (0.18)

EXHIBIT 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

- Registration Statement (Form S-3 No. 333-203072) of Cara Therapeutics Inc.
- Registration Statement (Form S-8 No. 333-203057) of Cara Therapeutics Inc., pertaining to the 2014 Equity Incentive Plan of Cara Therapeutics Inc., and
- 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 10, 2016, 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, 2015.

/s/ Ernst & Young LLP

Stamford, Connecticut
March 10, 2016

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 10, 2016

By: /s/ Derek Chalmers, Ph.D., D.Sc.
DEREK CHALMERS
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, Josef Schoell, 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 10, 2016

By: /s/ Josef Schoell
JOSEF SCHOELL
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, 2015, 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 Josef Schoell, 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 10, 2016

/s/ JOSEF SCHOELL
Name: Josef Schoell
Title: Chief Financial Officer
Date: March 10, 2016