Cara Therapeutics, Inc.
Form 10-K
March 28, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2013

OR

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

COMMISSION FILE NUMBER: 1-36279

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 Global Market**

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 x

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 x

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 x

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. x

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 x	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 x

The aggregate market value of the Registrant s Common Stock (the only common equity of the registrant) held by non-affiliates for the last business day of the Registrant s most recently completed second fiscal quarter: Not applicable because the Registrant s common equity was not publicly traded as of such date.

The number of shares outstanding of the Registrant s Common Stock, par value $.001 per share, as of March 21, 2014 was 22,592,414.

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CARA THERAPEUTICS, INC.

2013 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, ongo project, potential, should, will, or would, and or the negative of these terms, or other comparable terminology in 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 preclinical studies and clinical trials, including our planned Phase 3 clinical trials for I.V. CR845;
- our plans to develop and commercialize I.V. CR845 and our other product candidates, including Oral CR845;
- our ability to obtain and maintain regulatory approval of our product candidates, including I.V. CR845 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 performance of our current and future collaborators, including Maruishi and 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;

the size and growth of the potential markets for pain management, including the postoperative and chronic pain markets, and our other product candidates and our ability to serve those markets;

regulatory developments in the United States and foreign countries;

the rate and degree of market acceptance of any approved products;

our expectations regarding the period during which we will be an emerging growth company under the JOBS Act;

our use of the proceeds from our initial public 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;

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the success of competing drugs that are or become available;

the performance of third-party manufacturers and clinical research organizations; and

the purchases by certain of our existing principal stockholders and their affiliates in our initial public offering.

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 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 and have demonstrated efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics. Our most advanced product candidate, intravenous, or I.V., CR845, has demonstrated significant pain relief and a favorable safety and tolerability profile in three Phase 2 clinical trials in patients with acute postoperative pain. We plan to request an End of Phase 2 Meeting with the FDA in the second half of 2014 and begin Phase 3 registration trials for I.V. CR845 in the second half of 2014. We are also developing an oral version of CR845, or Oral CR845, for acute and chronic pain, for which we have successfully completed a Phase 1 clinical trial to demonstrate the ability to deliver CR845 orally.

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.

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On January 30, 2014, our registration statement on Form S-1 (File No 333-192230) was declared effective for our initial public offering (IPO), pursuant to which we registered the offering and sale of 5,750,000 shares of common stock (including 750,000 shares upon exercise of an option by the underwriters) at a public offering price of $11.00 per share for an aggregate offering price of $63.3 million. As a result of the IPO, we received net proceeds on February 5, 2014 of approximately $55.9 million from the sale of 5,750,000 shares of common stock, after deducting $7.4 million of underwriting discounts and commissions and estimated offering expenses payable by us.

According to IMS Health, an independent market research firm, the total U.S. market for pain management pharmaceuticals totaled $18.2 billion in 2012. The prescription pain management market in the United States is dominated by opioid analgesics, which, according to IMS Health data, represented 71% of the 341 million analgesic prescriptions written in 2012 and accounted for sales of $8.3 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 morphine, fentanyl and hydromorphone, 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 new chemical entity, CR845, is designed to produce pain relief by specifically stimulating kappa, rather than mu, opioid receptors. Moreover, 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. 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 because of their ability to provide pain relief while significantly reducing the incidence of opioid-related adverse events or abuse and addiction issues associated with currently approved mu opioid analgesics.

Our most advanced product candidate is an I.V. version of CR845 intended for the treatment of acute pain in a hospital setting. 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 CR845 has been documented in seven clinical trials, including four Phase 1 and three Phase 2 studies. CR845 has been administered to over 300 human subjects at single or repeat doses ranging from 0.002 mg/kg to 0.125 mg/kg over a 24 hour period in the form of I.V. infusion, I.V. bolus injection or oral capsule. 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

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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 addition to I.V. CR845, we are also developing an oral formulation of CR845 that we believe could be used to provide pain relief to patients with acute or chronic pain in an outpatient setting and also as an I.V.-to-oral transition, or step-down, therapy for hospital patients being prepared for discharge. We have successfully completed a Phase 1 trial of an oral capsule formulation of CR845 to establish oral bioavailability parameters and anticipate commencing additional Phase 1 clinical trials with an oral tablet formulation of CR845 in the first half of 2014. 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.

CR845 and CR701 were discovered by our scientists. We own six U.S. patents 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 two 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 hospital 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 in Japan and Chong Kun Dang Pharmaceutical Corp. in South Korea, which provide them the exclusive right to develop and market CR845 for certain indications within those territories. As of December 31, 2013, we had received approximately $24 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 2	Cara (worldwide, other than Japan and South Korea)
		Complete	Maruishi Pharmaceutical (Japan)
			Chong Kun Dang Pharmaceutical (South Korea)
Oral CR845	Acute & Chronic	Phase 1	Cara (worldwide, other than Japan and South Korea)
	Pain		Maruishi Pharmaceutical (Japan for acute pain indication only)
			Chong Kun Dang Pharmaceutical (South Korea)
CR701		Preclinical	Cara (worldwide)

Neuropathic &
Inflammatory Pain

The Market Opportunity

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

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illness. According to IMS Health, the total U.S. market for pain management pharmaceuticals was $18.2 billion in 2012. In 2011, according to Decision Resources, an independent industry research company, total sales for pain therapies in the seven major pharmaceutical markets, which include the United States, France, Germany, Italy, Spain, United Kingdom and Japan, exceeded $37 billion.

The severity of pain is the key factor in determining the appropriate therapy. Mild or mild-to-moderate pain is generally treated with OTC products, such as stand-alone oral formulations of aspirin, acetaminophen and ibuprofen. 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 71% of the nearly 341 million analgesic prescriptions written in 2012, accounting for $8.3 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). According to GBI Research, a research organization, the postoperative pain relief market, with sales of $5.9 billion in 2010, accounted for approximately 20% of the total pain management therapeutics market.

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

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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) and Opana (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 payors, 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.

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Our Product Candidates

Overview of CR845

CR845 is a peripherally-acting kappa opioid receptor agonist that we are developing for treatment of both acute and chronic pain. Our most advanced product candidate, I.V. CR845, has demonstrated significant pain relief and a favorable safety and tolerability profile in three Phase 2 clinical trials in patients with acute postoperative pain. Due to its selectivity for the kappa opioid receptor and ability to decrease mu opioid use, CR845 has demonstrated a consistent ability to decrease the acute opioid-related AEs of nausea and vomiting with no evidence of drug-related respiratory depression. CR845 has been administered to over 300 human subjects in Phase 1 and Phase 2 clinical trials as an intravenous infusion, rapid intravenous injection or oral capsule and was considered to be safe and well tolerated in these clinical trials.

We believe CR845-based products, if approved, have the potential to be attractive for patients with moderate-to-severe pain and their physicians due to the following attributes:

- novel, peripherally-acting, kappa opioid receptor mechanism of action;
- strong evidence of efficacy;
- potential for reducing mu opioid use and opioid-related 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 drug-drug interactions 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 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.

We are currently planning to request an End of Phase 2 meeting with the FDA in the second half of 2014 to discuss the Phase 3 pivotal trials for I.V. CR845 in acute pain which we expect to commence in the second half of 2014. We have successfully completed a Phase 1 clinical trial of a capsule formulation of Oral CR845 and are preparing to advance a tablet formulation of Oral CR845 into Phase 1 clinical trials in 2014.

I.V. CR845

Our most advanced product candidate, I.V. CR845, is an injectable version of our first-in-class, kappa opioid receptor-based peripheral analgesic which 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 demonstrated efficacy and tolerability in three randomized, double-blind, placebo-controlled Phase 2 clinical trials in patients undergoing soft tissue (laparoscopic hysterectomy) and hard tissue (bunionectomy) surgery. In both the laparoscopic hysterectomy and bunionectomy clinical trials, CR845 administration resulted in statistically significant reductions in pain intensity, as measured by summed pain intensity differences, or SPID, which is the FDA-recommended acute pain endpoint.

Phase 2b Laparoscopic Hysterectomy (CLIN2002)

Our *CLIN2002* clinical trial was a multicenter, double-randomized, double-blind, placebo-controlled trial conducted in 203 patients at 22 sites in the United States. The trial enrolled female patients, ages 21 to 65, scheduled for elective laparoscopic hysterectomy under general anesthesia. In this trial, patients were administered either placebo or one dose of 0.04 mg/kg I.V. CR845 preoperatively. Following surgery, if they were medically stable and had a pain intensity score ³40 on a 100 point pain scale based on the visual analog scale, or VAS, they were re-randomized to receive either placebo or one dose of 0.04 mg/kg I.V. CR845. Efficacy was measured using time-specific 24 hour pain intensity differences. Pain intensity, or PI, is measured at various times by asking patients to rate their pain on a 100-point scale, where 0 is absence of pain and 100

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is the worst possible pain. PID, or pain intensity difference, is the difference between the PI measured prior to treatment and at subsequent times of measurement. SPID, or the summed pain intensity difference, is the time-weighted sum of all of the PID scores, from the pretreatment level to a subsequent time of measurement, such as 24 hours after the pretreatment baseline pain measurement. Both PID and SPID are FDA-recognized endpoints for acute pain clinical trials. Additional endpoints included the amount of morphine consumption over 24 hours, time-specific total pain relief and patient global evaluation of study medication. Of the 203 patients that participated in the trial, 183 received a post-operative dose; however, two subjects did not record baseline pain scores and were not included in calculated PID and SPID values.

Accordingly, four treatment groups resulted from preoperative and postoperative randomization:

(1) I.V. CR845 administered both preoperatively and postoperatively (CR845/CR845);

(2) placebo administered preoperatively and I.V. CR845 administered postoperatively (Placebo/CR845);

(3) I.V. CR845 administered preoperatively and placebo administered postoperatively (CR845/Placebo); and

(4) placebo administered both preoperatively and postoperatively (Placebo/Placebo).

The CR845/CR845 group exhibited a statistically significant reduction in pain over a 24-hour time period, as indicated by an improvement in 0-24 hour mean SPID, compared to the Placebo/Placebo group (p£0.01). The Placebo/CR845 group also exhibited a statistically significant improvement in 0-24 hour mean SPID compared to the Placebo/Placebo group (p£0.05). The CR845/Placebo group exhibited an improved 0-24 hour mean SPID compared to the Placebo/Placebo group, but this difference did not reach statistical significance, which we believe was due to the small number of patients. Figure 1 below illustrates the 0-24 hour mean SPIDs of the four treatment groups listed above.

Clinical trial results are considered statistically significant when the probability of the results occurring by chance, rather than from the efficacy of the drug candidate, is sufficiently low. Statistical significance is measured by the probability value, or p-value. A clinical trial result with a p-value of equal to or less than 0.05 means that the probability of the same trial results occurring randomly or by chance is equal to or less than 5%, and is generally considered to be statistically significant.

Figure 1: Phase 2b Laparoscopic Hysterectomy Summed Pain Intensity Difference from 0-24 Hours ($SPID_{0-24}$) Following Postoperative Treatment

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Similar observations were made for different time periods after treatment. For example, over the 0-4 hour time period, in the CR845/CR845 group, there was a statistically significant 3.5-fold improvement in mean SPID values compared to the Placebo/Placebo group (p£0.05). In addition, over the 0-8, 0-12 and 0-16 time periods, patients in the Placebo/CR845 group also exhibited reduced pain intensity compared to the Placebo/Placebo group in a statistically significant manner (p£0.05), based on improved SPID values.

The mean PID from baseline at each time interval was numerically superior across all groups that received I.V. CR845 preoperatively and/or postoperatively relative to the Placebo/Placebo group. Compared to the Placebo/Placebo group, patients in the CR845/CR845 group exhibited an approximately 60% greater reduction in pain intensity at 24 hours, which was determined to be statistically significant (p£0.01), as well as statistically significant improvements for the 0-4, 0-8 and 0-16 hour time intervals (p£0.05, p£0.01 and p£0.05, respectively). Patients in the CR845/Placebo and Placebo/CR845 groups also exhibited statistically significant decreases in pain intensity for the 0-8 and 0-16 hour time intervals, compared to patients in the Placebo/Placebo group (p£0.05). Figure 2 below illustrates the PID relative to postoperative baseline in patients in the four treatment groups.

Figure 2: Phase 2b Laparoscopic Hysterectomy Pain Intensity Difference (PID) at Specific Times Relative to Postoperative Baseline Pain Intensity

* p£0.05
** p£0.01 for CR845/CR845
# p£0.05 for both Placebo/CR845 and CR845/Placebo.
Values represent mean ± SEM

At the same time points at which pain intensity measurements were taken, patients perceived pain relief scores were recorded using a 5 point subjective Likert scale (0-4), where zero corresponds to no relief and a score of four represents total relief. The TOTPAR score is calculated as the total pain relief score , which is a time-weighted sum of pain relief scores over any given time period following post-operative treatment with CR845 or

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placebo. TOTPAR is an FDA-recognized endpoint commonly used in acute pain trials. Mean TOTPAR scores were numerically superior across all intervals for the CR845/CR845 and Placebo/CR845 groups relative to the Placebo/Placebo group. The patients in the CR845/CR845 group and Placebo/CR845 exhibited statistically superior pain relief as compared to the Placebo/Placebo group within the first 2 hours following postoperative randomization, as indicated by increased mean $TOTPAR_{0-2}$ values (p£0.05). Figure 3 below depicts the mean TOTPAR scores for the first 2 hour period for each of the four treatment groups listed above.

Figure 3: Phase 2b Laparoscopic Hysterectomy Total Pain Relief Within the First 2 Hours ($TOTPAR_{0-2}$) Following Postoperative Treatment

* p£0.05
Values represent mean + SEM

Statistically significant improvements in pain relief were also reported in the CR845/CR845 and Placebo/CR845 groups compared to the Placebo/Placebo group for the 0-4 ($p<0.01$ for both groups), 2-4 ($p<0.04$ & $p<0.03$ for CR845/CR845 and Placebo/CR845 respectively) and 0-8 ($p<0.02$ for both groups) hour time periods. In addition, the improvement in mean TOTPAR also reached statistical significance for the 0-12 hour interval for the CR845/CR845 group relative to the Placebo/Placebo group (p£0.05).

Intravenous morphine was available as rescue medication to all treatment groups upon patient request. Calculations of morphine consumption per treatment group in the 2-24 hour period, after patients leave the post-anesthesia care unit, or PACU, indicated that patients in the CR845/CR845 group used approximately 45% less morphine than those in the Placebo/Placebo group (p£0.05), and patients in the Placebo/CR845 and CR845/Placebo groups used approximately 23% less morphine than those in the Placebo/Placebo group. Figure 4 below depicts the morphine usage in each of the treatment groups between hours 2-24.

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Figure 4: Phase 2b Laparoscopic Hysterectomy Morphine Consumption For 2-24 hours Post-Treatment in Patients

* p£0.05
Values represent mean + SEM

Concurrently with the observed reduction in morphine use, patients treated with I.V. CR845 exhibited a statistically significant lower incidence of opioid-related AEs through 24 hours after the start of the first infusion compared to patients who received only placebo. The incidence of nausea was reduced by approximately 50% (only 26.1% of patients administered CR845 experienced nausea as compared to 51.2% for placebo, p£0.001) and the incidence of vomiting was reduced nearly 80% (only 1.7% of patients administered CR845 experienced vomiting, as compared to 8.3% for placebo, p=0.035). There was also less pruritus, or itching sensation, reported in patients treated with CR845 compared to placebo. Figure 5 below depicts the percentage of patients reporting opioid-related adverse events of nausea, vomiting and pruritus.

Figure 5: Phase 2b Laparoscopic Hysterectomy Incidence of Opioid-Related Adverse Events Over 24 hours

* p=0.035
** p£0.001

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In addition to the reduction of opioid-related adverse events, a standard responder analysis indicated that a higher percentage of patients who received I.V. CR845 were characterized as Responders as compared to those receiving placebo (p=0.001). Responders included patients who rated their medication Excellent or Very Good and Non-Responders as those who rated their medication Fair or Poor . We believe that the lower overall pain intensity scores at the end of the study period for CR845-treated patients and the significant reduction in nausea and vomiting reported in these patients contributed to patients greater satisfaction with I.V. CR845 treatment compared to placebo. Figure 6 below depicts the number of patients classified as Responders or Non-Responders in the I.V. CR845-treated patients compared to the patients receiving only placebo.

Figure 6: Phase 2b Laparoscopic Hysterectomy Responder Analysis of Global Evaluation of Study Medication

* p=0.001

In this trial, intravenous administration of 0.04 mg/kg of I.V. CR845 preoperatively and/or postoperatively was safe and generally well tolerated. The placebo and CR845 treatment patient groups showed a similar overall incidence of treatment-emergent adverse events, or TEAEs, the majority of which were mild to moderate in severity. The most frequent TEAEs, reported in 10% or more of total patients, were nausea, hypotension, flatulence, blood sodium increase, or hypernatremia, and headache. There were no apparent consistent differences between CR845 and placebo groups in clinical laboratory results, vital signs, electrocardiogram, or oxygen saturation results, with the exception of blood sodium increase, which was evident only in CR845 treatment groups (14% of total patients). We believe that the increase in blood sodium levels, or hypernatremia, observed in CR845 treatment groups was likely a result of the aquaretic effect of I.V. CR845 at this dose and the replacement of fluid loss with sodium-containing intravenous solutions, rather than water or low to no sodium-containing fluids. In subsequent trials, fluid replacement with water or I.V. solutions with low or no sodium were used and no evidence of hypernatremia was observed.

Phase 2 Bunionectomy (CLIN2003)

A bunionectomy is a surgical procedure to remove a bunion, which is an enlargement of the joint at the base of the big toe and includes bone and soft tissue. The procedures typically result in intense pain requiring significant postoperative analgesic care, typically beginning with local anesthetic infusion and ongoing administration of a strong opioid, such as morphine or fentanyl, for several days afterwards.

Our *CLIN2003* clinical trial was a randomized, double-blind, placebo-controlled trial conducted in 51 patients following bunionectomy surgery at a single site in the U.S. The trial enrolled female and male patients, ages 18 years and older, scheduled for elective bunionectomy under regional anesthesia. Using a standard clinical

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trial protocol in which local anesthetic infusion was terminated on the day after surgery, patients were randomized into one of two treatment groups (CR845 or Placebo, in a 2:1 ratio) after reporting moderate-to-severe pain, defined as a pain intensity score ³ 40 on a 100-point pain scale. Patients randomized to receive I.V. CR845 were administered an I.V. injection at a dose of 0.005 mg/kg, and additional doses on an as-needed basis 30-60 minutes later, and then no more frequently than every 8 hours through a 48-hour dosing period. The results were analyzed separately for the per protocol population, or Completers , which includes only patients who completed the trial, and the modified Intent-to-Treat, or mITT, population, which includes Completers and all patients who discontinued the trial, or non-Completers . In the Completer group, CR845 treatment resulted in a statistically significant reduction in pain intensity compared to placebo, as measured by the SPID score over the initial 24 hour time period ($SPID_{0-24}$; $p<0.05$). This reduction in pain intensity after CR845 dosing was also statistically significant over a 36 hour time period ($SPID_{0-36}$, $p<0.03$), as well as over the entire two-day dosing period ($SPID_{0-48}$, $p<0.03$), compared to placebo-treated patients (see Figure 7a below). Numerical improvements in SPID scores in the CR845 group as compared to placebo were also evident across the same time periods when analyzing the mITT population of Completers together with non-Completers (see Figure 7b below).

Figure 7a: Phase 2 Bunionectomy Summed Pain Intensity Difference From 0-24 Hours ($SPID_{0-24}$), 0-36 Hours (p $SPID_{0-36}$) and 0-48 Hours ($SPID_{0-48}$) in Completer Population

Figure 7b: Phase 2 Bunionectomy Summed Pain Intensity Difference From 0-24 Hours ($SPID_{0-24}$), 0-36 Hours ($SPID_{0-36}$) and 0-48 Hours ($SPID_{0-48}$) in mITT Population (Completers Plus Non-Completers)

* p£0.05 One-sided Analysis of Variance with Treatment Group as a Main Effect (mean +/- s.e.m.)
** p£0.03 One-sided Analysis of Variance with Treatment Group as a Main Effect (mean +/- s.e.m.)

We believe that the Completer analysis is indicative of the actual efficacy of I.V. CR845, under conditions where patients are exposed to the drug as specified in the protocol, while the mITT analysis is indicative of the actual variability that will be encountered in the mITT populations. Our understanding of this variability will serve as the basis for determining the appropriate number of patients for enrollment in our Phase 3 clinical trials.

In this trial, we also measured mean PID from baseline at each time interval, which was numerically superior across the 48 hour trial period in the I.V. CR845 treatment group relative to the placebo group for both the Completer and mITT populations (see Figures 8a and 8b below). Statistically significant reductions in pain intensity differences in the CR845 group versus placebo were evident in the 0-12 hour time interval for both the Completer and mITT populations (p£0.01 and p£0.05 respectively) and for the 0-36 hour time interval for the Completer populations (p£0.05), consistent with the findings with the primary SPID endpoints.

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Figure 8a: Phase 2 Bunionectomy Pain Intensity Difference Relative to Baseline in CR845 and Placebo Completer Treatment Groups Across 48 Hours.

* p£0.05 (0-36 hours)
** p£0.01 (0-12 hours)

Figure 8b: Phase 2 Bunionectomy Pain Intensity Difference Relative to Baseline in CR845 and Placebo Treatment Groups in mITT Populations Across 48 Hours.

* p£0.05 (0-12 hours)

Fentanyl was available to both CR845 and placebo treatment groups upon patient request. While there was no difference in mean fentanyl use between the placebo and CR845 groups, the incidence of opioid-related AEs of nausea and vomiting was significantly reduced (by 60% and 80%, respectively; p£0.05) in patients who received CR845 compared to placebo during the 48 hour period after randomization (see Figure 9 below).

Figure 9: Phase 2 Bunionectomy CR845 Suppression of Nausea and Vomiting

* p£0.05

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We believe the ability of I.V. CR845 to reduce nausea and vomiting despite not meaningfully reducing fentanyl usage is due to a direct anti-vomiting or anti-nausea effect resulting from its kappa opioid agonist mechanism of action. We believe that the ability to provide postsurgical analgesia and simultaneously reduce opioid-related side effects will make I.V. CR845 an attractive treatment option for postoperative patients and their physicians.

In this bunionectomy trial, repeated intravenous administration of I.V. CR845 at a dose of 0.005 mg/kg was safe and generally well tolerated. The most frequent TEAEs (greater than 10%) observed in the CR845 treatment group were transient facial tingling and somnolence, a state of near-sleep. Of the seven cases of somnolence reported, the clinical trial s investigator reported four as mild and/or related to drug and three as moderate and/or not related to drug . Th mean plasma sodium concentration in CR845-treated patients exhibited an approximately 3% rise over 24 hours from baseline levels, but was not outside the normal physiological range at either 24 or 48 hours post-CR845 administration. This lack of clinically significant hypernatremia was likely a result of both utilizing a lower dose of I.V. CR845 and replacing transient fluid loss with oral water or sodium-free intravenous fluid. In addition, consistent with our prior studies, there was no evidence of acute psychiatric side effects that were observed with prior-generation CNS-active kappa opioid agonists.

Phase 2a Laparoscopic Hysterectomy (CLIN2001)

Our *CLIN2001* trial was a randomized, double-blind, placebo-controlled, proof-of-concept trial to evaluate the analgesic efficacy and safety of I.V. CR845 during the postoperative period in 114 patients undergoing laparoscopic hysterectomy. In the first of two cohorts, two single doses of I.V. CR845 (0.008 mg/kg and 0.024 mg/kg) were evaluated versus placebo in 68 patients who were maintained on patient-controlled analgesia, or PCA, morphine for 24 hours after surgery prior to randomization to receive treatment with CR845 or placebo. However, more than 50% of the patients (CR845 and placebo) in this cohort did not request any rescue medication before at least 4 hours after randomization and 30% of placebo patients required no narcotic for 24 hours after randomization. Therefore, it was concluded that the magnitude of pain the day after surgery appeared to be insufficient to allow separation between treatment groups and no clinical conclusions regarding the efficacy of I.V. CR845 could be made from this cohort.

In the second cohort, 46 patients were administered a single dose of I.V. CR845 (0.04 mg/kg) or placebo within three hours following recovery from surgery. In this group, CR845-treated patients exhibited statistically significant reductions in pain intensity up to six hours post-infusion versus placebo (p£0.05). Moreover, PCA morphine use was approximately 49% lower in the CR845-treated group compared to placebo starting at four hours post-infusion and lasting through an additional 12 hours (p£0.01) with a concomitant reduction in nausea and vomiting. The results for this proof-of-concept trial indicated that CR845 treatment could reduce pain intensity and morphine consumption post-surgery and informed the study timeline and design of the larger Phase 2 clinical trial (*CLIN2002*) described above.

In this Phase 2a Laparoscopic Hysterectomy clinical trial, administration of all three doses of I.V. CR845 was considered safe and generally well tolerated. Most of the TEAEs were comparable across groups, mild to moderate in severity, and nearly all were considered by the investigators to be unrelated, or to have an unlikely relationship, to study treatment. Transient facial tingling was the primary TEAE reported in CR845-treated groups in Cohort 1. Other AEs occurring in more than 10% in any group included headache, flatulence, nausea, pyrexia, urinary tract infection, dizziness and pruritus, most of which occurred in only one or two subjects per group.

CR845 Phase 1 Clinical Trials and Pre-clinical Studies

In addition to the three Phase 2 clinical trials, the safety of CR845 has been demonstrated in four Phase 1 clinical trials. CR845 was generally well tolerated in all of these clinical trials. The most common TEAEs across evaluated

populations were transient facial tingling or numbness, dizziness, fatigue and a transient increase in urine output in the absence of electrolyte loss, or aquaresis. Some of the subjects with aquaresis also exhibited an increase in heart rate upon standing up, or postural tachycardia, which was not accompanied by a decrease in

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blood pressure, resolved without intervention, and was classified as mild by the Investigator. We have demonstrated that this elevation in heart rate was a physiological consequence of the subject s fluid deficit rather than a direct effect of the drug. No other changes in vital signs, including supine pulse rate, blood pressure, respiratory rate, oral body temperature, or oxygen saturation were reported, nor were any clinically significant changes observed in electrocardiogram characteristics. In addition, the CNS adverse events characteristic of prior-generation CNS-active kappa agonists, such as acute psychiatric side effects, were not observed with CR845. The potential to cause sedation was assessed using the Ramsey Sedation Scale in the ascending dose-tolerance Phase 1 trial (Study 2048-001) of I.V. CR845, which included 54 subjects (17 on placebo; 37 on CR845). CR845 was considered to not cause sedation in this population of normal, healthy subjects in this trial.

A significant amount of preclinical work has been completed for CR845 in order to further define its characteristics. In standard preclinical pain models, CR845 attenuated acute and chronic visceral, inflammatory and neuropathic pain in a dose-dependent manner (see Table 1 below). The analgesic effect of CR845 was recordable within 15 minutes post-administration and lasted for up to 18 hours following single-dose administration. CR845 also decreased the production and release of pro-inflammatory mediators, which we believe is likely due to the direct activation of kappa opioid receptors expressed on immune cells that synthesize and secrete these substances.

Table 1: CR845 Exhibits a Broad Spectrum of Activity in Multiple Types of Industry Standard Preclinical Pain Models

Model		**Species**	**ED50 (I.V., mg/kg)**	**Duration of Action**
Somato Visceral Inflammatory Pain	Acetic Acid Writhing somatic and visceral pain	Mouse	0.07	>18 h
Chronic Inflammatory Pain	Complete Freund s Adjuvant mechanical hyperalgesia	Rat	0.08	>2 h
Acute Inflammatory Pain	Carrageenan mechanical hyperalgesia	Rat	0.3	>1h
Neuropathic Pain	L5/6 Spinal Nerve Ligation tactile allodynia	Rat	0.3	>8 h

The peripheral mechanism of action of CR845 has been supported preclinically by both biochemical measurement and functional pharmacological studies. In pharmacokinetic studies, animals administered analgesic and supra-analgesic doses of CR845 exhibited no measurable concentrations of drug in extracted brain tissue indicating that the CNS was not the site of action for CR845. Moreover, in standard preclinical pain models, such as the Chung Model of neuropathic pain, our scientists confirmed that the analgesic action of CR845 can be blocked with kappa opioid receptor antagonists administered directly to the local site of injury, indicating a peripheral site of action for CR845 (Figure 10 below). In the Chung Model , neuropathic pain is induced experimentally by ligating spinal nerves mediating sensation for a hind limb. This results in a type of neuropathic pain, referred to as allodynia. Experimental animals with allodynia exhibit a paw withdrawal reflex upon contact with a relatively thin filament on the injured site. Sets of different thickness filaments are used to test sensitivity, each of which is designed to produce a given force (in grams) upon bending after contact. By testing with these filaments, the minimum force to evoke a withdrawal response defines the paw withdrawal threshold. The nerve injury produces a marked reduction in paw withdrawal thresholds (increased sensitivity to force) in response to probing with the filaments. I.V. administration of CR845 reduces this neuropathic pain as demonstrated by a subsequent increase in the withdrawal threshold (see Figure 10

below). Administration of a low dose of the selective peripherally-acting kappa opioid receptor antagonist nor-binaltorphamine, or nor-BNI, into the plantar surface of the injured paw significantly reduces the effect of CR845, whereas injection of saline had no effect on the efficacy of CR845. Because nor-BNI was only able to block local peripheral kappa opioid receptors in this experiment, we believe these results show that the effect of CR845 is a result of activation of kappa opioid receptors located at the peripheral site of injury rather than in the CNS.

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Figure 10: Efficacy of CR845 in Chung Model of Neuropathic Pain is Blocked With Peripheral (Intrapaw) Administration of a Kappa Antagonist (norBNI) in Rats

* denotes p£0.001 compared to vehicle-treated controls (two-way analysis of variance).
Vehicle or Nor-BNI was administered intraplantarly (0.2 mg) 15 min prior to CR845
Injection (1 mg/kg).
N=6 male rats/group, mean ± SEM.

I.V. CR845 Phase 3 Clinical Development Plan

We are currently planning our Phase 3 clinical program to seek FDA approval for I.V. CR845 in the United States for the management of acute pain in a hospital setting. Based on guidance from the FDA, we believe that we will be required to complete two Phase 3 clinical trials, one in patients with pain resulting from soft tissue surgery and one in patients with pain resulting from hard tissue surgery. We believe that the primary efficacy endpoints will be the change in SPID at either 24 or 48 hours as compared to placebo. Recent trials conducted by other companies for FDA-approved acute pain drugs have run similar Phase 3 development programs in soft and hard tissue using either SPID 24 or SPID 48 as their endpoints. In addition to our two pivotal Phase 3 clinical studies for I.V. CR845 administered after surgery, we are also planning to run one optional supportive Phase 3 clinical trial with I.V. CR845 dosed both pre-surgery and post-surgery in patients undergoing either laparoscopic hysterectomy or bunionectomy surgery. In all three trials, patients will have access to morphine rescue medication throughout the trial. We are currently planning to request an End of Phase 2 meeting with the FDA in the second half of 2014 to discuss initiation of Phase 3 trials and expect to commence these trials in the second half of 2014 and file a New Drug Application, or NDA, with the FDA following the completion of these trials.

These planned clinical trials will be similar in design to our Phase 2 clinical trials:

CLIN3001: This clinical trial is expected to be a randomized, double-blind, placebo-controlled trial in approximately 600 female patients with postoperative pain after laparoscopic hysterectomy. The patients will be assigned to receive one of three doses of I.V. CR845 or placebo. The primary efficacy endpoint of the trial is expected to be the SPID at 24 hours. Secondary endpoints will include morphine use, SPID at other time points, TOPAR at 24 hours and occurrence of nausea and vomiting.

CLIN3002: This clinical trial is expected to be a randomized, double-blind, placebo-controlled trial in approximately 600 male or female patients with postoperative pain after bunionectomy surgery. The patients will be assigned to receive one of three doses of I.V. CR845 or placebo. The primary efficacy endpoint of the trial is expected to be the SPID at 48 hours. Secondary endpoints will include morphine use, SPID at other time points, TOPAR at 24 and 48 hours, and occurrence of nausea and vomiting.

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CLIN3003: This clinical trial is expected to be a supportive trial in approximately 450 patients with postoperative pain following either laparoscopic hysterectomy or bunionectomy surgery. This trial will be designed to compare the efficacy of I.V. CR845 when dosed both pre-surgery and post-surgery as compared with receiving I.V. CR845 only post-surgery. Patients will be randomized to receive either I.V. CR845 pre-surgery and post-surgery, or I.V. CR845 post-surgery only, or placebo. The primary efficacy endpoint of the trial is expected to be at either $SPID_{24}$ or $SPID_{48}$ hours. Secondary endpoints will include morphine use, SPID at other time points, TOPAR at 24 and 48 hours, and occurrence of nausea and vomiting.

To further confirm the lack of CNS euphoric effects and the non-abusability of CR845, we are also planning to complete a Human Abuse Liability Study in 2014. These studies are FDA-recommended and use non-dependent, recreational drug users to predict how likely it is that a test drug will be attractive to abusers. The results of this trial would be submitted as part of the I.V. CR845 NDA. Based on guidance from the FDA, we will require 1,500 total exposures to I.V. CR845 prior to filing an NDA. We believe our planned clinical trials and our clinical trials completed to date will result in sufficient exposures to support an NDA filing.

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 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.

We have developed a capsule formulation of CR845 using a third party proprietary formulation technology that is suitable for proof-of-concept clinical testing. A single center, randomized, double-blind placebo-controlled, escalating single oral dose, sequential group Phase 1 trial of Oral CR845 (Study 1001-PO) was conducted in 50 male volunteers administered with an enteric-coated capsule of CR845 (0.5, 1, 3, or 10 mg) or matched placebo. Oral bioavailability was estimated to be approximately 16%, with maximal plasma concentration and overall exposure increasing in a linear fashion at ascending doses, with a time to maximal concentration of approximately 3 hours (see Figure 11 below). The level of exposure at all doses was sufficient to activate peripheral kappa receptors, as indicated by an increase in serum prolactin, a known biomarker of kappa receptor activation. Oral CR845 was well tolerated and considered safe across all doses tested. Adverse events were similar to those reported after I.V. administration, with the addition of mild abdominal discomfort, which we believe to be related to the acidity of the excipients used in the oral capsule. None of the test subjects displayed any of the dysphoric or psychotomimetic side effects that have hindered the development of prior generations of centrally active kappa agonists. We believe this oral bioavailability, confirmed kappa activity at even the lowest capsule concentrations and early favorable safety profile to be an attractive basis for oral drug development.

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Figure 11: Phase 1a Pharmacokinetic Profiles of Ascending Concentrations of CR845 Capsules in Human Subjects.

Oral CR845 Clinical Development Plan

Having established a proof-of-concept for oral delivery of CR845 with a capsule version, we subsequently developed a tablet version which will provide greater predictability with respect to the relationship between amounts of drug administered and concentration in the blood, or pharmacokinetic predictability, as well as possess increased stability suitable for commercial shelf life. We have established drug substance stability and optimal pharmacokinetic characteristics for our tablet version in preclinical testing. We plan to conduct both single ascending and multiple ascending dose Phase 1 clinical trials in 2014 and, if the results of these trials are favorable, initiate a Phase 2a proof-of-concept trial in acute pain thereafter.

CR701 Overview

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.

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Our Strategy

Our strategy is to develop and commercialize a novel and first-in-class portfolio of peripheral-acting analgesics focused on kappa opioid receptor agonists, and subsequently 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 acute pain in the United States. We are currently planning a Phase 3 program for I.V. CR845 based on prior FDA guidance and will request an End of Phase 2 meeting in the second half of 2014 to discuss this with the FDA. We believe that we will be required to complete two Phase 3 clinical trials, one in patients with pain resulting from soft tissue surgery and one in patients with pain resulting from hard tissue surgery.

Build a sales and marketing organization to commercialize I.V. CR845 for acute pain in the hospital 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 sales and medical liaison organizations and 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 to proof-of-concept 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. We intend to advance Oral CR845 through our Phase 2a proof of concept trial and then 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. for patients who receive I.V. CR845 in the hospital and step down to the oral formulation as they leave the hospital.

Establish proof-of-concept for the utility of CR845 in additional, non-analgesic, clinical indications, such as pruritus. CR845 has exhibited potent anti-pruritic (anti-itch) properties in standard preclinical models of itch. Pruritus is a symptom of many systemic diseases, including hepatic, endocrine and neurological disorders, as well as a range of dermatological conditions. In addition, a pruritic condition, uremic pruritus, is prevalent among kidney dialysis patients and is resistant to both anti-histamine and steroid treatments. Previous clinical trials with other kappa agonists have demonstrated some efficacy in treating uremic pruritus. As a result, we believe that CR845 could have the potential to treat uremic pruritus. We have previously observed CR845 to have a good tolerability profile in end stage kidney disease patients. We intend to file an IND for CR845 this year to enable the initiation of a POC Phase 2 study in uremic pruritus.

Commercial Partnerships

Maruishi Pharmaceutical Co., Ltd.

In April 2013, we entered into a license agreement with Maruishi 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

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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 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 and a one-time sales milestone of one billion Yen (approximately $10 million) 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 agreement continues until terminated. Either we or Maruishi may terminate the 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 Chong Kun Dang Pharmaceutical Corp., or CKD, 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 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 license 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 license agreement. The agreement continues until CKD no longer has any obligation to pay us royalties on any product. Either we or CKD may terminate the agreement for the other party s breach of the agreement or bankruptcy. CKD may terminate the 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 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

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commercial organization in the United States to market and sell our I.V. product candidates in the hospital 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.

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. Six U.S. patents directed to CR845 have issued and 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. 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

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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 eight 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 and 8,536,131) with claims to compositions of a wide range of synthetic peptide amide kappa opioid agonists, including CR845 or 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, Japan, Malaysia, Mexico, New Zealand, Russia, Singapore and South Africa. 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, Canada, Israel, India and South Korea.

CR701

Our imidazoheterocycle cannabinoid compound patent portfolio, which is wholly owned by us, includes U.S. Patent Nos. 7,517,874 and 8,431,565; 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 and European and Eurasian regional patent applications have been filed based on the PCT application. The European regional patent has been granted as have national patents in Hong Kong, Israel, Malaysia, Mexico, New Zealand, Singapore and South Africa. These and any other patents resulting from the pending national patent applications, if issued, expire June 20, 2028.

Other Cara Patents and Patent Applications

We also own several other U.S. Patents including U.S. Patent Nos. 7,504,538; 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 and a pending U.S. patent application 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 in Canada, China, France, Germany, India, Italy, Japan, Mexico, Russia, Spain, South Korea 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 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

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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 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 payors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than 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 payors 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.

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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. 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 a 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 adjunctive analgesics, particularly in multimodal analgesic treatment approaches. Common adjunctive analgesics include: ketorolac, an injectable NSAID, which is available generically; Caldolor, an injectable ibuprofen marketed by Cumberland Pharmaceuticals; and Ofirmev, an injectable acetaminophen marketed by Cadence Pharmaceuticals.

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.

Oral CR845. We are developing Oral CR845 for use as a step-down therapy, as well as the management of moderate-to-severe chronic pain. The market for step-down therapies and for management of moderate-to-severe chronic pain is highly fragmented and includes numerous generic as well as brand name products, including oral formulations of NSAIDs and controlled-release mu opioids. Common NSAIDs include Celebrex, which is marketed by Pfizer, and naproxen and ibuprofen, which are available generically. Common 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; 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). Other product candidates in development are based on compounds with non-opioid mechanisms of action, including apremilast, an

anti-inflammatory compound being studied in Phase 3 clinical trials by Celgene.

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

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marketed by Endo Pharmaceuticals for PHN, and Qutenza, a capsaicin patch marketed by Acorda Therapeutics for PHN. Acorda Therapeutics is also developing a topical capsaicin cream, which is reportedly Phase 3 ready.

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;

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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.

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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.

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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.

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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 fraud and abuse laws restrict business practices in the biopharmaceutical industry. These laws include, among other things, anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations.

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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 Anti-Kickback Statute was also amended by the Health Care Reform Law, as defined above, 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.

The federal civil False Claims Act prohibits, 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 who is determined to have presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new 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 payors 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 payor.

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 omnibus rule published on January 25, 2013, imposes specified requirements 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

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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 for which payment is available under Medicare, Medicaid or the Children s Health Insurance Program (with certain exceptions) report annually to 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, with data collection required as of August 1, 2013, and reporting to CMS is required by March 31, 2014 (and by the 90th day of each subsequent calendar year). Disclosure of such information is to be made on a publicly available website beginning in September 2014.

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 penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, 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 payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide coverage for and establish adequate reimbursement levels for our product candidates. Government authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third party payors 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 payors 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

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our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental 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 payors to reimburse all or part of the associated healthcare costs. 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 payors.

Third party payors 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 payors are developing increasingly sophisticated methods of controlling healthcare costs. Third-party payors 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. Third-party payors 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. 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 payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. 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 payors 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.

Coverage, Reimbursement, and Pricing Developments

In the United States and some foreign jurisdictions, the legislative landscape 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 payors 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 Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase

demand for any products for which we receive marketing approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare

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beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Health Care Reform Law was passed in March 2010 and includes provisions that have the potential to substantially change healthcare financing by both governmental and private insurers. Among other cost containment measures, 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.

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. Under the Budget Control Act of 2011, as amended, federal budget sequestration Medicare payment reductions became effective on April 1, 2013 and automatically reduced payments under various government programs, including, for example, certain Medicare provider and supplier reimbursement payments. 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 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

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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 $7.2 million, $4.6 million and $8.7 million in 2011, 2012 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 subsequently advance the development of CR701.

Employees

As of December 31, 2013, we had 11 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.

Executive Officers

Our executive officers, their ages and their positions as of March 21, 2014 are set forth below:

Name	Age	Position
Derek Chalmers, Ph.D., D.Sc.	50	President, Chief Executive Officer and Director
Josef Schoell	63	Chief Financial Officer
Frédérique Menzaghi, Ph.D.	47	Vice President Research and Development
Michael E. Lewis, Ph.D.	62	Chief Scientific Advisor

Executive Officers

Derek Chalmers, Ph.D., D.Sc. Dr. Chalmers, one of our founders, has served as our President and Chief Executive Officer since September 2004 and has served as a member of our board of directors since July 2004. Dr. Chalmers has over 19 years experience in the biotechnology industry with increasing levels of corporate and business responsibilities. Prior to founding our company, Dr. Chalmers co-founded Arena Pharmaceuticals, Inc. (NASDAQ: ARNA), a drug discovery and development company, and served as its Vice President and Executive Director from June 1997 until May 2004. Dr. Chalmers holds a B.Sc. and Ph.D. in Pharmacology from the University of Glasgow.

Josef Schoell. Mr. Schoell has served as our Chief Financial Officer since May 2006. He joined us in May 2005 and served as our Controller between then and May 2006. Mr. Schoell has over 20 years of financial and accounting experience, including 18 years in the biotechnology industry. From 2003 until joining our company in May 2005, Mr. Schoell was a consultant with Robert Half Management Resources, a provider of accounting and financial professionals. From 1995 to 2002, he served as the Chief Financial Officer and Vice President Finance, of American Biogenetic Sciences Inc., a biotechnology company. Mr. Schoell received a B.S. in Accounting from the New York University Stern School of Business and is a Certified Public Accountant. Mr. Schoell is a member of the American

Institute of Certified Public Accountants and Financial Executives International.

Frédérique Menzaghi, Ph.D. Dr. Menzaghi, one of our founders, has served as our Vice President Research and Development since September 2004. Dr. Menzaghi has over 20 years of drug development and management experience in biotechnology. From 1999 to 2003, Dr. Menzaghi served as the Research Director of In Vivo Pharmacology at Arena Pharmaceuticals, Inc. (NASDAQ: ARNA) and from 2003 to 2004, was the Vice President Pharmacology and Business Development, at Psychogenics Inc., a preclinical central nervous system

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service provider. Dr. Menzaghi received her Ph.D. in Neurosciences from the Louis Pasteur University, Strasbourg, France and a M.Sc. in Clinical Psychology from the University of Nancy.

Michael E. Lewis, Ph.D. Dr. Lewis, one of our founders, has served as our Chief Scientific Advisor since September 2004, during which time he has provided services to us through BioDiligence Partners, Inc., or BDP, a consulting firm controlled by Dr. Lewis. Dr. Lewis also served as a member of our board of directors from September 2004 to July 2010. Prior to joining us, Dr. Lewis co-founded Arena Pharmaceuticals (NASDAQ: ARNA), and served as Arena s Chief Scientific Advisor from 1997 to 2004, also serving as a director of Arena from 1997 to 2000. Prior to co-founding Arena, Dr. Lewis co-founded and served as Chief Scientific Advisor of Adolor Corporation (NASDAQ: ADLR) from 1994 to 1997. Prior to that, Dr. Lewis co-founded Cephalon, Inc. (NASDAQ: CEPH), serving as Senior Scientist, Biology from 1988 to 1989, Director of Pharmacology from 1989 to 1992 and Senior Director of Scientific Affairs from 1992 to 1993. Dr. Lewis received a Ph.D. in Psychology from Clark University and post-doctoral training at the University of Cambridge, the National Institutes of Mental Health, and the University of Michigan, with a focus on opioid receptor research.

Each of our executive officers serves at the discretion of our board of directors and holds office until his or her successor is duly elected and qualified or until his or her earlier resignation or removal. There are no family relationships among any of our directors or executive officers.

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 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. CR845 with the goal of achieving regulatory approval. Since inception, we have incurred significant operating and net losses. Our net losses were $9.8 million, $6.3 million and $4.0 million for the years ended December 31, 2011, December 31, 2012 and December 31, 2013, respectively. As of December 31, 2013, we had an accumulated deficit of $62.5 million. Although we recognized $12.0 million of revenue during the year ended December 31, 2013 pursuant to our collaboration agreement with Maruishi Pharmaceutical Co., Ltd., or Maruishi, we nevertheless generated a net loss of $4.0 million for the period, and 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. CR845 and our other product candidates. In

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addition, we expect to incur significant sales, marketing and manufacturing expenses related to the commercialization of I.V. 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:

- commence our planned Phase 3 and other trials for I.V. CR845;
- initiate and enroll our Phase 1 clinical trials of Oral CR845;
- discover and develop additional product candidates;
- conduct late-stage clinical trials and seek regulatory approvals for any product candidates that successfully complete early clinical trials;
- increase our I.V. CR845 manufacturing batch sizes to satisfy FDA requirements for Phase 3 clinical trials and an NDA submission;
- establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval and that we choose not to license to a third party;
- maintain, expand and protect our 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 product development and planned 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 candidate, I.V. 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.

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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. CR845, is expensive. We will need to raise additional capital to:

- fund our future clinical trials if we encounter any unforeseen delays or difficulties in our planned development activities for I.V. CR845;
- 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 balance as of December 31, 2013, along with the net proceeds from our initial public offering, we will have sufficient funds to meet our projected operating requirements for at least the next 24 months, 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, we may not have sufficient financial resources to meet all of our objectives if I.V. CR845 is approved, which could require us to postpone, scale back or eliminate some, or all, of these objectives, including our potential launch activities relating to I.V. CR845. 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 1 and Phase 2 development of Oral CR845;

the rate of progress and costs of our efforts to prepare for the submission of an NDA 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;

defending our intellectual property and patent rights; 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

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financings, product supply revenue and royalties, 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.

Our lead product candidate, I.V. CR845, will require additional clinical development, 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, 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 payors;

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achieve appropriate 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. 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 Pharmaceutical Co., Ltd, or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or 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, for manufacturing of the finished clinical trial material. 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

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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. If we are unable to obtain an adequate supply of CR845 product from third-party suppliers to meet our obligations to Maruishi and/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 the product candidate. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs and consultants to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate s safety and efficacy for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities.

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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 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.

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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 have undesirable side effects that could delay or prevent their regulatory approval or commercialization.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to 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, if concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical testing, the FDA may order us to cease further development, decline to approve the drug or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug. The number of such requests for additional data or information issued by the FDA in recent years has increased, and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by I.V. CR845 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. Prolonged aquaresis can result in a negative fluid balance if the excreted water is not replaced by oral or intravenous water, and although we will recommend such prevention of dehydration, 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 dehydration, 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

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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.

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.

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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.

The FDA Amendments Act of 2007 implemented safety-related changes to product labeling and provided the FDA with expanded authority to require the adoption of a Risk Evaluation and Mitigation Strategy, or REMS, as part of an NDA or after approval. Many currently approved mu opioid receptor agonists require REMS. 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 safe and 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, 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. 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 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.

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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.

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Risks Related to the Commercialization of Our Product Candidates

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of pain. 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, Cadence Pharmaceuticals, Mallinckrodt, Actavis, Purdue Pharma, Janssen Pharmaceuticals, Celgene, Endo Pharmaceuticals, Depomed and Acorda Therapeutics.

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 payors 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 hospital 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

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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 payors. 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 payors 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;

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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 payors, 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 many 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 payors 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

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of our product candidates among physicians, patients and third-party payors. 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 payors, 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 $5.0 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.

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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 clinical research organizations, or CROs, to conduct our preclinical and clinical trials for our product candidates, including I.V. CR845, 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.

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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. 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 regulatory approval and/or commercializing delays or interruptions, as well as increased costs. For example, we have developed a formulation of Oral CR845 based on proprietary technology of Enteris Biopharma Inc., or Enteris. Under our agreement with Enteris, it is developing, testing and 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 will use its proprietary formulation technology for oral delivery of peptides to develop 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 to 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

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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 such agreements are terminated, 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 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.

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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 Business Commercial Partnerships section of this Annual Report on Form 10-K. 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.

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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, 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.

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Risks Related to Legal and Compliance Matters

If we fail to comply with federal and state healthcare laws, including fraud and abuse 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 payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients rights are and will be applicable to our business. We would be subject to healthcare fraud and abuse and patient privacy regulation by both the federal government and the states in which we conduct our business. The laws 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, 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 payors that are false or fraudulent;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new 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 payor (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 the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its 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, such as health plans, healthcare clearinghouses and healthcare providers;

federal transparency laws, including the federal Physician Payment Sunshine Act, that requires disclosure of payments and other transfers of value provided to physicians and teaching hospitals; 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 payor, 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.

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Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under the U.S. federal Anti-Kickback Statute, 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 Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, which we refer to collectively as the Health Care Reform Law among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. 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 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 civil and criminal penalties, damages, fines, exclusion from participation in U.S. federal or state health care programs, 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 and fraud 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 third-party payors fail to provide coverage and adequate coverage 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 payors. Such third-party payors 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 payors. 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 payors, 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 payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future

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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 new legislation, regulatory proposals and healthcare payor 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 the potential to significantly change health care financing and the delivery of health care in the United States. Among the provisions of the Health Care Reform Law of greatest 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, that began in 2011;

- 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;

- addresses 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 beginning in April 2010 and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, 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 requirements under the federal Physician Payment Sunshine Act, and its implementing regulations, for drug manufacturers and others to report information related to payments and other transfers of value made or distributed to physicians and teaching hospitals as well as ownership investment interests held by physicians and their immediate family members;

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, such recommended reports could begin in 2014;

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establishment of a Center for Medicare & Medicaid Innovation at the Centers for Medicare & Medicaid Services to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending, that began on January 1, 2011; 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. 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 payors. 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.

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, and at this time, the full effect that the Health Care Reform Law would have on our business remains unclear.

In addition, there have been a number of other legislative and regulatory proposals aimed at changing the pharmaceutical industry. In particular, California has enacted legislation that requires development of an electronic pedigree to track and trace each prescription drug at the saleable unit level through the distribution system. California s electronic pedigree requirement is scheduled to take effect on a staggered basis, with 50 percent of a manufacturer s products by January 1, 2015 and the remaining 50 percent by 2016. Compliance with California and future federal or state electronic pedigree requirements may increase our operational expenses and impose significant administrative burdens. As a result of these and other new proposals, we may determine to change our current manner of operation, provide additional benefits or change our contract arrangements, any of which could have a material adverse effect on our business, financial condition and results of operations.

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

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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 payors, that an adequate level of reimbursement will be available or that the third-party payors 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 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 employee fraud or other misconduct. Misconduct by employees 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. Employee 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 employee 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.

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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.

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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;

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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.

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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.

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Risks Related to Employee Matters, Managing Growth and Operating as a Public Company

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

As of December 31, 2013, we had only 11 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.

We will incur increased costs as a result of operating as a public company.

As a public company, and particularly after we are no longer an emerging growth company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and

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corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

Since we have completed our initial public offering, we are now 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 will be required to furnish a report by our management on our internal control over financial reporting. Commencing with our fiscal year ending December 31, 2014, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Form 10-K filing for that year, as required by Section 404. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm.

To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. Prior to our initial public offering, we were never required to test our internal controls within a specified period, and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

We may 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 are not able to comply with the requirements of Section 404 in a timely manner, or 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

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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

Prior to our initial public offering in January 2014, there was no established public market for our stock and a public market may not be sustained or may be illiquid and, therefore, you may have difficulty selling your shares.

Prior to our initial public offering in January 2014, there was no public market for our common stock. Although our common stock is listed on The NASDAQ Global Market, we cannot assure you that an active trading market will be sustained or that any trading market will be liquid. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for investors in our common stock to sell shares without depressing the market price for the shares or to sell the shares at all.

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, our stock price has been volatile, and it is likely that the trading price of our common stock will continue to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- delays in the commencement, enrollment and ultimate completion, of Phase 3 clinical trials for I.V. CR845;
- 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;

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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 do not publish research or reports, or 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 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:

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;

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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.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

As of February 28, 2014, our executive officers, directors and 5% stockholders and their respective affiliates beneficially owned an aggregate of approximately 56.8% of our outstanding common stock. As a result, these stockholders have significant influence and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This concentration of ownership could delay or prevent any acquisition of our company on terms that other stockholders may desire.

Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the price at which shares were sold in our initial public offering and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other stockholders.

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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 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.

As of February 28, 2014, we have outstanding 22,592,414 shares of common stock. Of these shares, 5,386,365 of the 5,750,000 shares sold in our initial public offering and 46,609 additional shares that were outstanding prior to our initial public offering are freely tradable. An additional 17,159,440 shares of common stock, including an aggregate of 363,635 shares acquired by certain of our pre-IPO principal stockholders and their affiliated entities, will be available for sale in the public market beginning July 29, 2014 upon the expiration of lock-up agreements between some of our stockholders and the underwriters for our initial public offering, subject, in the case of our affiliates, to the volume, manner of sale and other limitations of Rule 144, and an additional 494,676 shares issuable upon exercise of options and warrants vested as of the expiration of the lock-up period will be eligible for sale at that time, subject, in the case of our affiliates, to the volume, manner of sale and other limitations of Rule 144. The representatives of the underwriters may release these stockholders from their lock-up agreements with the underwriters at any time and without notice, which would allow for earlier sales of shares in the public market. Sales of stock by these stockholders could have a material adverse effect on the market price of our common stock.

In addition, on February 12, 2014, we filed a registration statement on Form S-8 registering the issuance of 2,090,160 shares of common stock subject to options or other equity awards issued or reserved for future issuance under our 2004 Plan and our 2014 Plan. Shares registered under this registration statement on Form S-8 will be available for sale in the public market subject to vesting arrangements and exercise of options, the lock-up agreements described above and, in the case of our affiliates, the restrictions of Rule 144. Holders of approximately 15,929,477 shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as amended, or the Securities Act, subject to the 180-day lock-up arrangement described above. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act. Any sales of securities by these stockholders, or the expectation that such sales may occur, could have a material adverse effect on the trading 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 as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, 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, (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, 2013, we had federal and state net operating loss carryforwards of approximately $55.6 million and $50.7 million, respectively, and we also had federal and state research and development tax credit carryforwards of approximately $2.3 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, 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 following our initial public offering, 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.

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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. We believe that our current facilities are suitable and adequate to meet our current needs. We intend to add new facilities or expand existing facilities as we add employees, and we believe that suitable additional or substitute space will be available as needed to accommodate any such expansion of our operations.

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.

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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. Prior to our IPO, there was no public market for our common stock. As a result, we have not set forth quarterly information with respect to the high and low prices for our common stock for the two most recent fiscal years.

The last reported sale price of our common stock as reported on The NASDAQ Global Market on March 21, 2014 was $17.15 per share.

Stockholders

As of March 21, 2014, there were 160 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.

Recent Sales of Unregistered Securities

From December 28, 2012 until February 28, 2013, we issued unsecured convertible promissory notes to 68 purchasers in an aggregate principal amount of approximately $4.0 million. Sixty-one of these purchasers opted to convert an aggregate of approximately $3.9 million in principal and interest under the promissory notes into an aggregate of 2,692,291 shares of our Series D convertible preferred stock on September 18, 2013, and an aggregate of approximately $300,000 in principal and interest was repaid to the promissory noteholders who did not opt to convert such notes prior to the notes maturity date. Upon completion of our initial public offering, these shares of Series D convertible preferred stock converted into 1,076,916 shares of our common stock.

In April 2013, we issued and sold an aggregate of 2,105,263 shares of Junior A convertible preferred stock to Maruishi at $3.80 per share for aggregate consideration of approximately $8.0 million. Upon completion of our initial public offering, these shares of Junior A convertible preferred stock converted into 842,105 shares of our common stock.

No underwriters were used in the foregoing transactions. The sales of securities described in paragraphs (1) through (8) above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act as transactions by an issuer not involving a public offering and/or Rule 506 promulgated under the Securities Act. All of the

purchasers in these transactions represented to us in connection with their purchase that they were acquiring the shares for investment and not distribution, and that they could bear the risks of the investment and could hold the securities for an indefinite period of time. Such purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration or an available exemption from such registration. All of the foregoing securities are deemed restricted securities for the purposes of the Securities Act.

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Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

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. The managing underwriters were Stifel, Nicolaus & Company, Incorporated and Piper Jaffray & Co and the co-managers were Canaccord Genuity Inc., Needham & Company, LLC and Janney Montgomery Scott LLC.

As a result of the initial public offering, we received net proceeds on February 5, 2014 of approximately $55.9 million from the sale of 5,750,000 shares of common stock, after deducting $7.4 million of underwriting discounts and commissions and estimated offering expenses payable by us. 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.

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

The following selected financial data as of and for the years ended December 31, 2011, December 31, 2012 and December 31, 2013 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. 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. As we qualify as an emerging growth company per the JOBS Act, certain selected financial data as ordinarily required under SEC Regulation S-K Item 301 for the years ended December 31, 2010 and 2009 have been omitted.

	Year Ended December 31,		
	2011	2012	2013
	(in thousands, except share and per share data)		
Statement of Operations Data:			
Total revenue	$	$ 1,190	$ 11,964
Operating expenses:			
Research and development	7,159	4,597	8,685
General and administrative	2,407	2,829	3,516
Total operating expenses	9,566	7,426	12,201
Operating loss	(9,566)	(6,236)	(237)
Total other expense	(275)	(66)	(3,756)
Loss before benefit from income taxes	(9,841)	(6,302)	(3,993)
Benefit from income taxes	35	31	30
Net loss	$ (9,806)	$ (6,271)	$ (3,963)
Net loss available to common stockholders	$ (9,806)	$ (6,271)	$ (3,072)
Net loss per share:			
Basic and Diluted	$ (3.03)	$ (1.90)	$ (0.74)
Weighted average shares:			
Basic and Diluted	3,235,743	3,299,993	4,133,138

	As of December 31,		
	2011	2012	2013
Balance Sheet Data:			
Cash and cash equivalents	$ 4,097	$ 1,117	$ 12,357
Total assets	10,685	5,537	18,083
Deferred revenue			3,475

Total liabilities	4,581	3,098	6,572
Total convertible preferred stock	58,168	58,522	65,586
Total stockholders deficit	(52,064)	(58,133)	(54,075)

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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 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 and have demonstrated efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects associated with currently available pain therapeutics. Our most advanced product candidate, intravenous, or I.V., CR845, has demonstrated significant pain relief and favorable tolerability in three Phase 2 clinical trials in patients with acute postoperative pain. We are currently planning to request an End of Phase 2 meeting with the FDA in the second half of 2014 to discuss initiation of Phase 3 trials which we expect to initiate in the second half of 2014. We are also developing an oral version of CR845, or Oral CR845, for acute and chronic pain, for which we have successfully completed a Phase 1 clinical trial to demonstrate the ability to deliver CR845 orally.

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, 2013, we have received net proceeds of $65.9 million from the sale of various series of convertible preferred stock, $3.6 million from the issuance of convertible promissory notes and $3.8 million from the issuance of long-term debt. In addition to our financing activities, we have received aggregate payments of $28.9 million pursuant to license agreements related to CR845 and an earlier product candidate for which development efforts ceased in 2007. In April 2013, we received $15.0 million as an upfront payment pursuant to a license agreement with Maruishi Pharmaceutical Co., Ltd., or Maruishi, in connection with the license of rights to CR845 in Japan. In 2012, we received aggregate upfront and milestone payments of $1.2 million, net of foreign taxes, pursuant to a license agreement with Chong Kun Dang Pharmaceutical Corporation, or CKD, in connection with the license of rights to CR845 in South Korea.

Since inception, we have incurred significant operating and net losses. Our net losses were $9.8 million, $6.3 million and $4.0 million for the years ended December 31, 2011, December 31, 2012 and December 31, 2013, respectively. We generated a net loss of $4.0 million for the year ended December 31, 2013, although we recognized $12.0 million of revenue for the period in connection with the Maruishi license, and we expect to continue to incur significant expenses and operating and net losses over at least the next several years. As of December 31, 2013, we had an

accumulated deficit of $62.5 million. 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 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:

- initiate our planned Phase 3 clinical trials of I.V. CR845;

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- 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.

To fund further operations, we will need to raise capital in addition to the net proceeds of our initial public offering. As of December 31, 2013, we had cash and cash equivalents of approximately $12.4 million. We may obtain additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. We may not be able to raise additional capital on terms acceptable to us, or at all, and any failure to raise capital as and when needed could compromise our ability to execute on our business plan. Although it is difficult to predict future liquidity requirements, we believe that the net proceeds from our initial public offering (see Recent Developments, below) and our existing cash and cash equivalents as of December 31, 2013, together with interest thereon, will be sufficient to fund our operations for at least the next 24 months. However, our ability to successfully transition to profitability will be dependent upon achieving a level of revenues adequate to support our cost structure. We cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

Recent Developments

Initial Public Offering

On February 5, 2014, we closed the initial public offering of our common stock. We sold a total of 5,750,000 shares in the offering, including 750,000 shares upon the exercise in full by the underwriters of their option to purchase additional shares. The aggregate public offering price was $63.3 million, and we received net proceeds of approximately $55.9 million from the offering, after deducting $7.4 million of underwriting discounts and commissions and estimated offering expenses payable by us.

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 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 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 will provide Maruishi specific clinical development services for CR845 in Maruishi s field of use. Under the terms of the 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. 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 license 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.

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In April 2012, we entered into a license agreement with CKD under which we granted CKD an exclusive license to develop, manufacture and commercialize drug products containing CR845 in South Korea. We and CKD are 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 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 license agreement. 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, as well as license agreements for CR665, our first generation drug program for which development efforts have ceased. During 2012, we also received $0.6 million, net of foreign taxes, of clinical development milestone payments under our license agreement with CKD. During the year ended December 31, 2013, we recognized revenue of $0.1 million from the sale of clinical compound and $11.9 million under the Maruishi license agreement. However, we have not received any other significant development or regulatory milestone payments, or 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 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 and the FDA approval process. 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.

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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 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, 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 expenses related to services associated with maintaining compliance with NASDAQ listing rules and SEC requirements, 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.

Interest Expense, Net

Interest expense, net, consists of interest paid on debt instruments, amortized deferred financing costs and amortized debt discount, as offset by any interest income earned on our cash and cash equivalents. 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.

Other Income (Expense), Net

Other income (expense), net, consists of the change in the fair value of the investor rights and obligations related to our Series D Convertible Preferred Stock financing, which we refer to as the investor right/obligation. This financing was completed in four tranches of $5.0 million, $3.0 million, $2.0 million and $5.0 million in July 2010, March 2011, July 2011 and August 2011, respectively. In connection with the first closing of the Series D Convertible Preferred Stock financing, we granted investors the right and, pursuant to the terms and conditions of the financing, such investors committed, to purchase additional shares of Series D Convertible Preferred Stock in

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subsequent closings. In accordance with accounting principles generally accepted in the United States (U.S. GAAP or GAAP), the investor right/obligation represented a free-standing financial instrument, which we recorded at its fair value of $733,900 as a liability on the date of the first closing. We then marked this liability to market at each subsequent reporting date that the instrument remained outstanding, reflecting the increase (decrease) in the value of the investor right/obligation as other (expense) income in our results of operations. Because the rights and obligations related to the Series D Convertible Preferred Stock financing terminated upon the final closing of Series D Convertible Preferred Stock in August 2011, we no longer record other income (expense) in connection with the investor right/obligation from that point forward.

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, 2012 and December 31, 2013

The following table sets forth our results of operations for the years ended December 31, 2012 and 2013 (in thousands).

	Year Ended December 31, 2012	2013	Period-to-Period Change
Revenue	$ 1,190	$ 11,964	$ 10,774
Cost and expenses:			
Research and development	4,597	8,685	4,088
General and administrative	2,829	3,516	687
	7,426	12,201	4,775
Operating loss	(6,236)	(237)	5,999
Interest (expense), net	(66)	(3,756)	(3,690)
Loss before benefit from income taxes	(6,302)	(3,993)	2,309
Benefit from income taxes	31	30	(1)
Net loss	$ (6,271)	$ (3,963)	$ 2,308

Revenue

Revenue increased $10.8 million, to $12.0 million, for the year ended December 31, 2013, compared to the same

period of 2012. The increase was primarily a result of our recognition as revenue of a portion of the upfront payment received upon entry into the license agreement with Maruishi in April 2013. The revenue recognized in the 2012 period represents the revenue recognized in connection with the license agreement with CKD in April 2012.

Research and development expenses

Research and development expenses increased by $4.1 million to $8.7 million, for the year ended December 31, 2013, compared to the same period of 2012. The increase was primarily the result of a $3.7 million increase in direct preclinical studies and CR845 clinical trial costs, a $0.3 million increase in payroll and recruiting costs, a $0.3 million increase in consultant services in support of preclinical studies and clinical trials and a $0.1 million increase in travel costs, partially offset by a $0.2 million decrease in depreciation and amortization expense. The increase in CR845 clinical trial costs resulted primarily from the completion of the Phase 2 bunionectomy trial, the Phase 1 IV CR845 renal impairment trial and preclinical costs for formulation and studies related to oral tablets of CR845.

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The following table summarizes our research and development expenses by product candidate for the year ended December 31, 2012 and 2013 (in thousands):

	Year Ended December 31,	
	2012	2013
External research and development expenses:		
I.V. CR845	$ 1,570	$ 3,995
Oral CR845	351	1,826
Internal research and development expenses	2,676	2,864
Total research and development expenses	$ 4,597	$ 8,685

General and administrative expenses

General and administrative expenses increased by $0.7 million, to $3.5 million, for the year ended December 31, 2013, compared to the same period of 2012. The increase was primarily attributable to an increase in accounting, legal and consulting professional fees of $0.8 million, including consulting services incurred in connection with the Maruishi license agreement of $0.4 million and preparation for the Company s initial public offering, and a $0.1 million increase in payroll and recruiting costs, partially offset by a decrease of $0.3 million related to a loss on sale of assets in the year ended December 31, 2012.

Interest expense, net

Interest expense, net, increased by $3.7 million, to $3.8 million, for the year ended December 31, 2013, compared to the same period of 2012. The increase in expense was primarily due to $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.

Comparison of the years ended December 31, 2011 and 2012

The following table sets forth our results of operations for the years ended December 31, 2011 and 2012 (in thousands).

	Year Ended December 31,		Period-to-Period Change
	2011	2012	
Revenue	$	$ 1,190	$ 1,190
Cost and expenses:			
Research and development	7,159	4,597	(2,562)
General and administrative	2,407	2,829	422
	9,566	7,426	(2,140)

Operating (loss)	(9,566)	(6,236)	3,330
Other (expense):			
Interest (expense), net	(95)	(66)	29
Other (expense):	(180)		180
	(275)	(66)	209
Loss before benefit from income taxes	(9,841)	(6,302)	3,539
Benefit from income taxes	35	31	(4)
Net loss	$ (9,806)	$ (6,271)	$ 3,535

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Revenue

Revenue for the year ended December 31, 2012 was $1.2 million, consisting of $0.6 million, net of foreign taxes, related to the upfront payment received from CKD and $0.6 million, net of foreign withholding taxes, received from CKD upon the achievement of clinical development milestones under the agreement. We did not generate any revenue in 2011.

Research and development expenses

Research and development expenses decreased by $2.6 million, to $4.6 million, for the year ended December 31, 2012, compared to 2011. The decrease resulted primarily from a $2.1 million decrease in expenses related to our Phase 2 clinical trial of I.V. CR845, which was completed in early 2012, a $0.1 million decrease in payroll costs as a result of a workforce reduction effected in 2011 and a $0.1 million reduction in depreciation expense.

The following table summarizes our research and development expenses by product candidate for the years ended December 31, 2011 and 2012 (in thousands):

	Year Ended December 31,	
	2011	2012
External research and development expenses:		
I.V. CR845	$ 3,123	$ 1,570
Oral CR845	874	351
Internal research and development expenses	3,162	2,676
Total research and development expenses	$ 7,159	$ 4,597

General and administrative expenses

General and administrative expenses increased by $0.4 million, to $2.8 million, for the year ended December 31, 2012, compared to 2011. The increase resulted primarily from a $0.3 million increase in consulting expenses as a result of the engagement of consultants for business development efforts and a $0.3 million loss on the sale of fixed assets consisting of idle laboratory equipment, partially offset by a $0.2 million reduction in payroll costs as a result of a workforce reduction in 2011.

Interest expense, net

Interest expense, net, decreased by $29 thousand to $66 thousand for the year ended December 31, 2012, compared to 2011. The decrease resulted primarily from a reduction in the outstanding principal balance on our loan from Connecticut Innovations Inc., or CII.

Other expense

Other expense for the year ended December 31, 2011 was $0.2 million. This expense related to an increase in the fair value of the investor right/obligation. There was no corresponding other expense incurred in 2012, as the investor right/obligation was terminated upon the date of the last closing of our Series D Convertible Preferred Stock financing in 2011.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception and through December 31, 2013, we have raised an aggregate of $102.5 million to fund our operations, including primarily $28.9 million received under our license agreements, primarily with Maruishi and CKD, $65.9 million of net proceeds from the sale of shares of our convertible preferred stock and $7.4 million of net proceeds from debt financings. As of December 31, 2013, we had $12.4 million in cash and cash equivalents. On February 5, 2014, we received net proceeds of $55.9 million from our initial public offering.

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In addition to our existing cash and cash equivalents, we are potentially eligible to earn a significant amount of milestone payments and royalties under our license agreements with Maruishi and CKD. 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. As a result, our receipt of any such amounts is uncertain at this time and we may never receive any of these amounts.

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.

Connecticut Innovations, Inc. Term Loan

In September 2007, we entered into a $4.0 million term loan with CII. The loan bore interest at 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 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 all outstanding amounts under the loan from CII, including accrued interest, in April 2013. The warrant remains outstanding and expires September 25, 2014.

Funding Requirements

Our primary uses of capital have been, and we expect will continue to be, compensation and related expenses, third-party clinical research and development services, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs.

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;

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achieving meaningful penetration in the markets which we seek to serve; and

obtaining adequate coverage or reimbursement by third parties, such as commercial payors 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 the early stages of 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 may require additional capital beyond our currently anticipated amounts and this additional capital may not be available when needed, on reasonable terms, or at all. To the extent that we raise additional capital through the future sale of equity or 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 our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents as of December 31, 2013, after giving effect to the net proceeds we received in the initial public offering, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 24 months, without giving effect to any potential milestone payments we may receive under our collaboration agreements. 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 cash flows for the years ended December 31, 2011, 2012 and 2013 (in thousands):

	Year Ended December 31,		
	2011	**2012**	**2013**
Net cash (used in) provided by operating activities	$ (6,845)	$ (6,031)	$ 2,829
Net cash provided by (used in) investing activities	45	511	(5)

Net cash provided by financing activities	9,136	2,540	8,416
Net (decrease) increase in cash and cash equivalents	$ 2,336	$ (2,980)	$ 11,240

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Net cash (used in) provided by operating activities

Net cash provided by operating activities was $2.8 million for the year ended December 31, 2013. Net cash provided by operating activities for the period consisted primarily of net loss of $4.0 million, a $2.4 million cash inflow from net changes in operating assets and liabilities and $4.4 million of net non-cash charges. 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, partially offset by deferred rent costs of $0.2 million. The net change in operating assets and liabilities primarily consisted of $3.5 million of deferred revenue from the Maruishi license transaction and a $0.7 million increase in accounts payable and accrued expenses, partially offset by an increase of $1.7 million, primarily related to costs of our initial public offering included in prepaid and other current assets.

Net cash used in operating activities was $6.0 million for the year ended December 31, 2012. Net cash used in operating activities for the period consisted primarily of net loss of $6.3 million and a $0.9 million cash outflow from net changes in operating assets and liabilities, partially offset by $1.2 million of net non-cash charges. Net non-cash charges primarily consisted of $1.0 million of depreciation and amortization expense, a $0.3 million loss on the sale of assets and $0.1 million of stock-based compensation expense, partially offset by deferred rent costs of $0.2 million. The net change in operating assets and liabilities primarily consisted of a $1.3 million decrease in accounts payable and accrued expenses, comprised mainly of clinical trial payments, partially offset by a decrease in restricted cash of $0.3 million.

Net cash used in operating activities was $6.8 million for the year ended December 31, 2011. Net cash used in operating activities for the period consisted primarily of net loss of $9.8 million, partially offset by a $1.7 million cash inflow from net changes in operating assets and liabilities and $1.2 million of net non-cash charges. Net non-cash charges primarily consisted of $1.2 million of depreciation and amortization expense, a $0.2 million increase in the fair value of our investor right/obligation and $0.1 million of stock-based compensation expense, partially offset by deferred rent costs of $0.2 million. The net change in operating assets and liabilities primarily consisted of a $1.5 million increase in accounts payable and accrued expenses, comprised mainly of clinical trial costs incurred, and a decrease in restricted cash of $0.3 million.

Net cash provided by (used in) investing activities

Net cash used in investing activities was $5 thousand for year ended December 31, 2013, representing the purchase of office equipment. Net cash provided by investing activities was $0.5 million and $45 thousand for the year ended December 31, 2012 and the year ended December 31, 2011, respectively, which generally consisted of the proceeds received on the sale of laboratory equipment, which, for the year ended December 31, 2011, was partially offset by cash used to purchase office equipment.

Net cash provided by financing activities

Net cash provided by financing activities was $8.4 million for the year ended December 31, 2013, which 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.

Net cash provided by financing activities was $2.5 million for the year ended December 31, 2012, which consisted primarily of $2.5 million of net proceeds from the issuance of convertible promissory notes, $0.4 million of net proceeds from the sale of Junior Convertible Preferred Stock to CKD, $0.1 million of proceeds from the exercise of stock options and $0.1 million of proceeds from the sale of common stock, partially offset by $0.4 million in principal payments under our loan agreement with CII.

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Net cash provided by financing activities was $9.1 million for the year ended December 31, 2011, which consisted primarily of the net proceeds of $10.0 million from the issuance of Series D Convertible Preferred Stock, partially offset by $0.8 million in principal payments made under our loan agreement with CII.

Contractual Obligations. The following summarizes our significant contractual obligations as of December 31, 2013 (in thousands).

		Payment due by period			
Contractual Obligations	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**More than 5 years**
Operating lease obligations	$ 3,399	$ 860	$ 1,799	$ 740	$

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 U.S. 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 license revenue 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; delivery has occurred or services have been rendered; our price to the customer is fixed or determinable and collectability is reasonably assured.

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.

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We record revenue related to these agreements in accordance with ASC 605-25, *Revenue Recognition Multiple-Element Arrangements*. In order to account for these agreements, we identify the deliverables included within 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.

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.

Our license agreements have 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 milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone in accordance with ASC 605-28, *Revenue Recognition Milestone Method*. 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, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment.

We generally consider non-refundable development and regulatory milestones that we expect to be achieved as a result of our efforts during the period of our performance obligations under the license and research

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agreements to be substantive and recognize them as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If not considered to be substantive, we initially defer milestones and recognize them over the remaining term of our performance obligations. If no such performance obligation exist, milestones that are not considered substantive because we do not contribute effort to the achievement of such milestones 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 and non-employees as compensation for services performed. Employee awards of stock-based compensation are accounted for in accordance with ASC 718, *Stock Compensation*. ASC 718 requires all share-based payments to employees, including grants of employee stock options, to be recognized in the Statements of Operations based on their grant date fair values. We estimate the grant date fair value of stock options using the Black-Scholes option valuation model. Prior to our initial public offering, 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 our common stock values used in the Black-Scholes model. Since our initial public offering, our common stock value is based on the closing price of our common stock on the date of grant on The NASDAQ Global Market. The Black-Scholes model requires us to make judgments about the following: (1) the risk-free rate, which is based on the U.S. Treasury yield curve in effect at the time of grant; (2) the expected life of stock options granted to employees, which was 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;* (3) the expected life of stock options granted to non-employees, which was determined using the options maximum contractual life of ten years and (4) expected volatility, which was based on an analysis of guideline companies in accordance with ASC 718.

We account for options issued to non-employees under ASC 505, *Equity-Based Payments to Non-Employees*. As such, the value of such options is periodically re-measured and income or expense is recognized during their vesting terms. Compensation cost relating to awards with service-based graded vesting schedules is recognized using the straight-line method.

We granted 517,000 stock options during the year ended December 31, 2011 but did not issue any stock options during the years ended December 31, 2012 or December 31, 2013.

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 U.S. 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 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.

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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 959,547 shares of common stock. We determined that this conversion represented an extinguishment of the preferred stock under U.S. 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 date 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 are accounting for the values allocated to the respective license arrangements in accordance with our revenue recognition policies described above.

Preferred Stock Valuations

As described above, 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.

Common Stock Valuation

Prior to our initial public offering, 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

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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 have not issued shares of common stock, options or warrants to purchase common stock or, except as described above, any other instruments convertible into common stock, since January 1, 2012, other than the issuance of common stock upon the exercise of outstanding stock options. However, we have estimated the fair value of our common stock as of December 31, 2011 and December 31, 2012 for purposes of revaluing outstanding options held by consultants and adjusting compensation expense accordingly during the vesting period of those options as required by U.S. 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, 2011 valuation, we employed a combination of the income approach, described above, and the market approach, which took into account the value implied by our July 2010 Series D Preferred Stock financing. For our December 31, 2012 valuation, 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.

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 will 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.***

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of December 31, 2012 and 2013, we had cash and cash equivalents of $1.1 million and $12.4 million, respectively. We generally hold our cash equivalents in interest-bearing money market accounts. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term maturities of our cash equivalents and the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our cash equivalents.

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*.

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

None.

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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.

Management s Report on Internal Control Over Financial Reporting

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

Changes in Internal Control Over Financial Reporting

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, 2013 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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

None.

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PART III

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

The following table sets forth information concerning our directors as of March 21, 2014.

Name	Age	Position
Derek Chalmers, Ph.D., D.Sc.	50	President, Chief Executive Officer and Director
Ed Hurwitz[(1)(2)(3)]	50	Director
Charles Moller, Ph.D.[(1)(2)(3)]	60	Director
Dean Slagel	44	Director
Martin Vogelbaum[(1)(2)(3)]	50	Director

(1) Member of our audit committee.
(2) Member of our nominating and corporate governance committee.
(3) Member of our compensation committee.

Directors

Derek Chalmers, Ph.D., D.Sc. Dr. Chalmers biography is included under the caption *Business Executive Officers* in Item 1 of this Annual Report. Dr. Chalmers qualifications to sit on our board of directors include his leadership, executive, managerial and business experience, historical knowledge of our company and his background and experience in the biotechnology industry, including having been a founder of a prior biotechnology company.

Ed Hurwitz. Mr. Hurwitz has served as a member of our board of directors since November 2006. Mr. Hurwitz is currently a Managing Director of Precision BioVentures, LLC, an investment and business consulting firm. Mr. Hurwitz was a Director of Alta Partners, a venture capital firm, from 2002 to 2013. He continues to serve as a Director of Alta BioPharma Management III, LLC and as a consultant to Alta Partners Management VIII, LLC. Mr. Hurwitz currently serves as a director of MacroGenics, Inc., a publicly held company. Mr. Hurwitz also served as a director of Sunesis Pharmaceuticals, Inc., a publicly held company, from April 2009 to September 2013 and serves as a director of one privately-held company. Mr. Hurwitz s financial and scientific expertise, as well as his deep understanding of the biotechnology industry provide him with the qualifications and skills to serve on our board of directors.

Dr. Charles Moller. Dr. Moller has served as a member of our board of directors since June 2008. Dr. Moller is a founder and General Partner of Devon Park Bioventures, L.P., a venture capital organization founded in February 2006. In 1990, Dr. Moller joined Radnor Venture Partners, a TL Ventures predecessor fund. For 16 years, from 1992 to 2008, he led the TL Ventures biotechnology group and was responsible for evaluating, selecting and managing biotech companies in TL Ventures portfolio. Dr. Moller earned a Ph.D. in Immunology from the University of Pennsylvania and was a post-doctoral fellow at the Roche Institute for Molecular Biology. He also holds a B.A. in Chemistry from Pomona College. Dr. Moller s experience working with life sciences companies, scientific expertise and his experience working in the venture capital industry provide him with the qualifications and skills to serve on our board of directors.

Dean Slagel. Mr. Slagel has served as a member of our board of directors since February 2005. Mr. Slagel is the Managing Director of Esperante BV and Esperante AB, life sciences venture investment companies founded in

September 2004 and June 2005, respectively. From September 1995 to September 2004, Mr. Slagel served as the Global Business Development Director of Ferring Pharmaceuticals, a specialty biopharmaceutical group then based principally in the UK, France and Denmark. He received an MBA from the ENPC Business School in Paris, France, in 2000. Mr. Slagel s more than 20 years of international pharmaceutical industry and life science companies investment experience provide him with the qualifications and skills to serve on our board of directors.

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Martin Vogelbaum. Mr. Vogelbaum has served as a member of our board of directors since July 2010. Mr. Vogelbaum has served as a partner of Rho Ventures since 2005 and primarily focuses on investments in biotechnology, biopharmaceuticals and medical devices. He has more than 19 years of experience investing in the life sciences sector, having been involved with companies at all stages of development, including co-founding more than a half dozen companies. Mr. Vogelbaum currently serves as a director of Nephrogenex, Inc. From 2007 to 2010, Mr. Vogelbaum served as a member of the board of directors of Middlebrook Pharmaceuticals, Inc. Prior to his venture capital career, he was a research associate in the bone marrow transplantation unit at Memorial-Sloan Kettering Hospital, where he conducted research in graft-versus-host-disease (GVHD). Mr. Vogelbaum received his A.B. in biology and history from Columbia University. Mr. Vogelbaum s experience in the life sciences industry as a venture capitalist provides him with the qualifications and skills to serve on our board of directors.

Each of our executive officers serves at the discretion of our board of directors and holds office until his or her successor is duly elected and qualified or until his or her earlier resignation or removal. There are no family relationships among any of our directors or executive officers.

Board Composition

Our business and affairs are managed under the direction of our board of directors, which currently consists of five directors. In accordance with our amended and restated certificate of incorporation, our board of directors is divided into three classes with staggered three-year terms. At each annual general meeting of stockholders, the successors to directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election. Our directors are divided among the three classes as follows:

The Class I directors are Mr. Hurwitz and Dr. Moller, and their terms will expire at our first annual meeting of stockholders to be held following completion of our initial public offering;

The Class II directors are Mr. Slagel, and his term will expire at our second annual meeting of stockholders to be held following completion of our initial public offering; and

The Class III directors are Mr. Vogelbaum and Dr. Chalmers, and their terms will expire at our third annual meeting of stockholders to be held following completion of our initial public offering.

We expect that additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class will consist of one-third of the directors. The division of our board of directors into three classes with staggered three-year terms may delay or prevent a change of our management or a change in control.

Committees of the Board of Directors

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee, each of which has the composition and responsibilities described below. From time to time, the board may establish other committees to facilitate the management of our business.

Audit Committee

Our audit committee reviews our internal accounting procedures and consults with and reviews the services provided by our independent registered public accountants. Our audit committee consists of three directors, Mr. Vogelbaum, Mr. Hurwitz and Dr. Moller, and our board of directors has determined that each of them is independent within the meaning of the applicable stock exchange listing requirements and the independence requirements contemplated by Rule 10A-3 under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Mr. Vogelbaum is the chairman of the audit committee and our board of directors has determined

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that Mr. Hurwitz is an audit committee financial expert as defined by SEC rules and regulations. Our board of directors has determined that the composition of our audit committee meets the criteria for independence under, and the functioning of our audit committee complies with, the applicable requirements of the Sarbanes-Oxley Act, applicable stock exchange listing requirements and SEC rules and regulations. We intend to continue to evaluate the requirements applicable to us and we intend to comply with the future requirements to the extent that they become applicable to our audit committee. The principal duties and responsibilities of our audit committee include:

- appointing and retaining an independent registered public accounting firm to serve as independent auditor to audit our financial statements, overseeing the independent auditor s work and determining the independent auditor s compensation;
- approving in advance all audit services and non-audit services to be provided to us by our independent auditor;
- establishing procedures for the receipt, retention and treatment of complaints received by us regarding accounting, internal accounting controls, auditing or compliance matters, as well as for the confidential, anonymous submission by our employees of concerns regarding questionable accounting or auditing matters;
- reviewing and discussing with management and our independent auditor the results of the annual audit and the independent auditor s review of our quarterly financial statements; and
- conferring with management and our independent auditor about the scope, adequacy and effectiveness of our internal accounting controls, the objectivity of our financial reporting and our accounting policies and practices.

Compensation Committee

Our compensation committee reviews and determines the compensation of all our executive officers. Our compensation committee consists of three directors, Mr. Vogelbaum, Mr. Hurwitz and Dr. Moller, each of whom is a non-employee member of our board of directors as defined in Rule 16b-3 under the Exchange Act. Mr. Vogelbaum is the chairman of the compensation committee. Our board of directors has determined that the composition of our compensation committee satisfies the applicable independence requirements under, and the functioning of our compensation committee complies with the applicable requirements of, stock exchange listing rules and SEC rules and regulations. We intend to continue to evaluate and intend to comply with all future requirements applicable to our compensation committee. The principal duties and responsibilities of our compensation committee include:

- establishing and approving, and making recommendations to the board of directors regarding, performance goals and objectives relevant to the compensation of our chief executive officer, evaluating the performance of our chief executive officer in light of those goals and objectives and setting, or recommending to the full board of directors for approval, the chief executive officer s compensation, including incentive-based and equity-based compensation, based on that evaluation;

setting the compensation of our other executive officers, based in part on recommendations of the chief executive officer;

exercising administrative authority under our stock plans and employee benefit plans;

establishing policies and making recommendations to our board of directors regarding director compensation;

reviewing and discussing with management the compensation discussion and analysis that we may be required from time to time to include in SEC filings; and

preparing a compensation committee report on executive compensation as may be required from time to time to be included in our annual proxy statements or annual reports on Form 10-K filed with the SEC.

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Nominating and Corporate Governance Committee

The nominating and corporate governance committee consists of three directors, Mr. Vogelbaum, Mr. Hurwitz and Dr. Moller. Mr. Vogelbaum is the chairman of the nominating and corporate governance committee. Our board of directors has determined that the composition of our nominating and corporate governance committee satisfies the applicable independence requirements under, and the functioning of our nominating and corporate governance committee complies with the applicable requirements of, stock exchange listing standards and SEC rules and regulations. We will continue to evaluate and will comply with all future requirements applicable to our nominating and corporate governance committee. The nominating and corporate governance committee s responsibilities include:

- assessing the need for new directors and identifying individuals qualified to become directors;
- recommending to the board of directors the persons to be nominated for election as directors and to each of the board s committees;
- assessing individual director performance, participation and qualifications;
- developing and recommending to the board corporate governance principles;
- monitoring the effectiveness of the board and the quality of the relationship between management and the board; and
- overseeing an annual evaluation of the board s performance.

Code of Business Conduct and Ethics for Employees, Executive Officers and Directors

We have adopted a Code of Business Conduct and Ethics, or the Code of Conduct, applicable to all of our employees, executive officers and directors, which is available on our website at *www.caratherapeutics.com*. The nominating and corporate governance committee of our board of directors is responsible for overseeing the Code of Conduct and must approve any waivers of the Code of Conduct for employees, executive officers and directors. We expect that any amendments to the Code of Conduct, or any waivers of its requirements, will be disclosed on our website.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934 requires persons who own more than ten percent of a registered class of our equity securities and our directors and executive officers to file with the SEC initial reports of ownership and reports in changes in ownership of any Cara Therapeutics equity securities. Because we were not publicly traded in 2013, no reports were required to be filed in 2013.

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

This section discusses the material components of the executive compensation program for our executive officers who are named in the 2013 Summary Compensation Table below. In 2013, our president and chief executive officer and our three other highest-paid executive officers, which we collectively refer to as our named executive officers, were as follows:

Derek Chalmers, Ph.D., our President and Chief Executive Officer;

James B. Jones, M.D., PharmD, FACEP, our former Chief Medical Officer;

Frédérique Menzaghi, Ph.D., Vice President Research and Development; and

Josef Schoell, our Chief Financial Officer.

This discussion contains forward-looking statements that are based on our current plans, considerations, expectations and determinations regarding future compensation programs. Actual compensation programs that we adopt in the future may differ materially from the currently planned programs summarized in this discussion.

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2013 Summary Compensation Table

The following table provides information regarding the compensation earned during the years ended December 31, 2012 and 2013 by our named executive officers.

Name and Principal Position	Year	Salary ($)	Bonus ($)	Option Awards ($)	Non-Equity Incentive Plan Compensation($)	Total ($)
Derek Chalmers, Ph.D., D.Sc.[1]	2013	400,000	40,000			440,000
President and Chief Executive Officer	2012	400,000				400,000
James B. Jones, M.D., PharmD, FACEP[2]	2013	223,000	30,000			253,000
Former Chief Medical Officer	2012	325,000				325,000
Frédérique Menzaghi, Ph.D.	2013	275,000	30,000			305,000
Vice President Research and Development	2012	275,000				275,000
Josef Schoell	2013	190,000	15,000			205,000
Chief Financial Officer	2012	190,000				190,000

(1) Dr. Chalmers is also a member of our board of directors but does not receive any additional compensation in his capacity as a director.
(2) Dr. Jones employment with the company terminated on September 6, 2013.

Outstanding Equity Awards as of December 31, 2013

The following table sets forth information regarding outstanding stock options held by our named executive officers as of December 31, 2013.

Name	Grant Date	Number of Securities Underlying Unexercised Options Exercisable	Number of Securities Underlying Unexercised Options Unexercisable	Option Exercise Price ($)	Option Expiration Date
Derek Chalmers, Ph.D. *President and Chief Executive Officer*	11/7/2007	40,000		$ 2.48	11/7/2017
James B. Jones, M.D., PharmD, FACEP *Former Chief Medical Officer*	4/28/2011	93,800		$ 0.85	9/6/2014[1]
Frédérique Menzaghi, Ph.D	7/11/2005	20,000		$ 0.25	7/11/2015

Vice President Research and Development	11/7/2007	20,000		$ 2.48	11/7/2017
	8/14/2008	10,000		$ 2.25	8/14/2018
	10/15/2010	31,666	8,334(2)	$ 2.05	10/15/2020
Josef Schoell	5/2/2005	40,000		$ 0.25	7/11/2015
Chief Financial Officer	8/29/2006	8,000		$ 0.78	9/29/2016
	11/7/2007	12,000		$ 2.48	11/7/2017
	8/14/2008	4,000		$ 2.25	8/14/2018
	9/8/2011	5,625	4,375(2)	$ 0.85	9/8/2021

(1) Dr. Jones employment with us terminated effective September 6, 2013. Dr. Jones has through September 6, 2014 to exercise the option.

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

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2014 Stock Option Grants

In connection with our initial public offering, we granted stock options on the date of the pricing of the initial public offering to Dr. Chalmers, Dr. Menzaghi and Mr. Schoell for 80,000, 40,000 and 50,000 shares of our common stock, respectively. All such option grants have an exercise price equal to the initial public offering price per share in our initial public offering ($11.00 per share). These options will vest over a four-year period as follows: 25% of the shares underlying the option will vest on the first anniversary of the date of grant, with the remainder vesting in equal monthly installments over the 36 months thereafter.

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

In February 2014, we entered into employment agreements with Dr. Chalmers, Dr. Menzaghi and Mr. Schoell, following the completion of our initial public offering. Under these employment agreements, which supersede offer letters that we had previously entered into with these officers, the executive officers respective annual salaries and target annual bonuses are:

Executive Officer	Base Salary	Target Bonus (as a % of Base Salary)
Dr. Chalmers	$ 440,000	50%
Dr. Menzaghi	$ 302,500	35%
Mr. Schoell	$ 209,000	35%

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

cause means that we have determined in our sole discretion that any of the following occurred: (a) the executive officer s commission of a felony; (b) the executive officer s act or omission constituting dishonesty, fraud, immoral, or disreputable conduct that causes material harm to us; (c) the executive officer s violation of a company policy that causes material harm to us; (d) the executive officer s material breach of the employment agreement, or of any provision of any other agreement between the executive officer and us which, if curable, is not cured within 30 days after notice thereof is given to the executive officer, or (e) the executive officer s breach of fiduciary duty;

good reason means any of the following without the executive officer s prior written consent: (a) the assignment to the executive officer of duties or responsibilities that would result in the material diminution of the executive officer s then-current position, with the exception of certain situations involving the acquisition of the company; (b) a reduction of the executive officer s annual base salary by greater than 30%, except in a situation in which the base salaries of other similarly situated employees are accordingly reduced; or (c) any request that the executive officer relocate to a new principal base of operations that would increase the executive officer s one-way commute distance by more than 100 miles, unless the executive officer accepts the relocation opportunity.

change in control means any of the following: (a) any person becomes the owner, directly or indirectly, of securities representing more than 50% of the combined voting power of the company other than through a merger, consolidation or similar transaction, subject to specified exceptions; (b) a merger or consolidation, unless the holders of our outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing more than 50% of the voting power of the company or other entity surviving such transaction, subject to specified exceptions; (c) a sale, lease, exclusive license or other disposition of all or substantially all of our assets, other than the transfer of our assets to an entity of which our stockholders own more than 50% of the voting power, subject to specified exceptions; or (d) the directors at the time of our initial public offering, or

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the incumbent board, cease to constitute at least a majority of the board of directors, provided, that new directors that are approved or recommended by the majority of the incumbent board will be considered to be a member of the incumbent board for this purpose.

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

Scenario and Executive	Salary and Payment of Employer Health Insurance Continuation[1]	Bonus[1]	Acceleration of Unvested Equity Awards
More than 12 Months Following a Change in Control:			
Dr. Chalmers	12 months	Prorated Target Bonus	None
Dr. Menzaghi	6 months	Prorated Target Bonus	None
Mr. Schoell	6 months	Prorated Target Bonus	None
Within 12 Months Following a Change in Control:			
Dr. Chalmers	12 months	Prorated Target Bonus	Full Acceleration[2]
Dr. Menzaghi	6 months	Prorated Target Bonus	Full Acceleration[2]
Mr. Schoell	6 months	Prorated Target Bonus	Full Acceleration[2]

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

(2) The executive officer will receive accelerated vesting of all of his or her then unvested equity awards, if any.

Equity Incentive Plans

2014 Equity Incentive Plan

Our board of directors and our stockholders approved and adopted our 2014 Equity Incentive Plan, or 2014 Plan, in January 2014. Our board of directors may amend or suspend the 2014 Plan at any time, although no such action may impair the rights under any then-outstanding award without the holder s consent. We will obtain stockholder approval for any amendments to the 2014 Plan as required by law. No incentive stock options may be granted under the 2014 Plan after the tenth anniversary of the effective date of the 2014 Plan.

Types of Awards. The 2014 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights, performance stock awards and other forms of equity compensation, or collectively, stock awards. Additionally, the 2014 Plan provides for the grant of performance cash awards. Incentive stock options may be granted only to employees. All other awards may be granted to employees, including officers, non-employee directors, and consultants.

Share Reserve. Initially, the aggregate number of shares of our common stock that may be issued pursuant to stock awards under the 2014 Plan is 1,600,000 shares. Additionally, the number of shares of our 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 our capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by our board of directors. The maximum number of shares that may be issued pursuant to the exercise of incentive stock options under the 2014 Plan is 30,000,000 shares.

Section 162(m) Limits. No person may be granted awards covering more than 3,000,000 shares of our common stock under the 2014 Plan during any calendar year pursuant to an appreciation-only stock award. An appreciation-only stock award is a stock award whose value is determined by reference to an increase over an exercise or strike price of at least 100% of the fair market value of our common stock on the date of grant. A stock option with an exercise price equal to the value of the stock on the date of grant is an example of an appreciation-only award.

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Additionally, no person may be granted in a calendar year a performance stock award covering more than 3,000,000 shares or a performance cash award having a maximum value in excess of $3.0 million. Such limitations are designed to help assure that any deductions to which we would otherwise be entitled with respect to such awards will not be subject to the $1 million limitation on the income tax deductibility of compensation paid per covered executive officer imposed by Section 162(m) of the Code.

Reversion of Shares. If a stock award granted under the 2014 Plan expires or otherwise terminates without being exercised in full, or is settled in cash, the shares of our common stock not acquired pursuant to the stock award will again become available for subsequent issuance under the 2014 Plan. In addition, the following types of shares under the 2014 Plan will become available for the grant of new stock awards under the 2014 Plan:

- shares that are forfeited to or repurchased by us prior to becoming fully vested;
- shares withheld to satisfy income and employment withholding taxes; and
- shares used to pay the exercise price or purchase price of a stock award.

Shares issued under the 2014 Plan may be previously unissued shares or reacquired shares bought on the open market.

Administration. Our board of directors, or a duly authorized committee thereof, has the authority to administer the 2014 Plan. Our board of directors may also delegate to one or more of our officers the authority to (1) designate employees (other than other officers) to be recipients of certain stock awards, and (2) determine the number of shares of common stock to be subject to such stock awards. Subject to the terms of the 2014 Plan, our board of directors or the authorized committee, referred to herein as the plan administrator, determines recipients, dates of grant, the numbers and types of stock awards to be granted and the terms and conditions of the stock awards, including the period of their exercisability and vesting schedule applicable to a stock award. Subject to the limitations set forth below, the plan administrator will also determine the exercise price, strike price or purchase price of awards granted and the types of consideration to be paid for the award.

The plan administrator has the authority to modify outstanding awards under our 2014 Plan. Subject to the terms of our 2014 Plan, the plan administrator has the authority to reduce the exercise, purchase or strike price of any outstanding stock award, cancel any outstanding stock award in exchange for new stock awards, cash or other consideration, or take any other action that is treated as a repricing under generally accepted accounting principles, with the consent of any adversely affected participant.

Stock Options. Incentive and nonstatutory stock options are granted pursuant to stock option agreements adopted by the plan administrator. The plan administrator determines the exercise price for a stock option, within the terms and conditions of the 2014 Plan, provided that the exercise price of an incentive stock option and nonstatutory stock option generally cannot be less than 100% of the fair market value of our common stock on the date of grant. Options granted under the 2014 Plan vest at the rate specified by the plan administrator.

The plan administrator determines the term of stock options granted under the 2014 Plan, up to a maximum of ten years. Unless the terms of an optionee s stock option agreement provide otherwise, if an optionee s service relationship with us, or any of our affiliates, ceases for any reason other than a termination for cause or other than a termination because of disability or death, the optionee may exercise the vested portion of any options for a period of three months

following the cessation of service. If an optionee s service relationship with us, or any of our affiliates, ceases due to disability or death or an optionee dies within a specified period following cessation of service, the optionee or a beneficiary may exercise the vested portion of any options for a period of 12 months in the event of disability and 18 months in the event of death. In the event of a termination of an optionee s service for cause, the option will terminate upon the optionee s cessation of service and the optionee may not exercise the option following such termination. The option term may be further extended in the event that exercise of the option following termination of service is prohibited by applicable securities laws, or the sale of any common stock received upon exercise of the option would violate our insider trading policy. In no event, however, may an option be exercised beyond the expiration of its term.

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Acceptable consideration for the purchase of common stock issued upon the exercise of a stock option will be determined by the plan administrator and may include cash or check, a broker-assisted cashless exercise, the tender of common stock previously owned by the optionee, a net exercise of the option if it is a nonstatutory stock option, and other legal consideration approved by the plan administrator.

Unless the plan administrator provides otherwise, options generally are not transferable except by will, the laws of descent and distribution, or pursuant to a domestic relations order. An optionee may designate a beneficiary, however, who may exercise the option following the optionee s death.

Tax Limitations on Incentive Stock Options. Incentive stock options may be granted only to our employees. The aggregate fair market value, determined at the time of grant, of shares of our common stock with respect to which incentive stock options that are exercisable for the first time by an optionee during any calendar year under all of our stock plans may not exceed $100 thousand. No incentive stock option may be granted to any person who, at the time of the grant, owns or is deemed to own stock possessing more than 10% of our total combined voting power or that of any of our affiliates unless the option exercise price is at least 110% of the fair market value of the stock subject to the option on the date of grant, and the term of the incentive stock option does not exceed five years from the date of grant.

Restricted Stock Awards. Restricted stock awards are granted pursuant to restricted stock award agreements adopted by the plan administrator. Restricted stock awards may be granted in consideration for cash or check, past or future services rendered to us or our affiliates, or any other form of legal consideration. Shares of common stock acquired under a restricted stock award may, but need not, be subject to a share repurchase option in our favor in accordance with a vesting schedule to be determined by the plan administrator. Rights to acquire shares under a restricted stock award may be transferred only upon such terms and conditions as set by the plan administrator.

Restricted Stock Unit Awards. A restricted stock unit is a promise by us to issue shares of our common stock, or to pay cash equal to the value of shares of our common stock, equivalent to the number of units covered by the award at the time of vesting of the units or thereafter. Restricted stock unit awards are granted pursuant to restricted stock unit award agreements adopted by the plan administrator. Restricted stock unit awards may be granted in consideration for any form of legal consideration. A restricted stock unit award may be settled by cash, delivery of stock, a combination of cash and stock as deemed appropriate by the plan administrator, or in any other form of consideration set forth in the restricted stock unit award agreement. Additionally, dividend equivalents may be credited in respect to shares covered by a restricted stock unit award. Except as otherwise provided in the applicable award agreement, restricted stock units that have not vested will be forfeited upon the participant s cessation of continuous service for any reason.

Stock Appreciation Rights. A stock appreciation right entitles the participant to a payment equal in value to the appreciation in the value of the underlying shares of our common stock for a predetermined number of shares over a specified period. Stock appreciation rights are granted pursuant to stock appreciation right agreements adopted by the plan administrator. The plan administrator determines the strike price for a stock appreciation right which cannot be less than 100% of the fair market value of our common stock on the date of grant. Upon the exercise of a stock appreciation right, we will pay the participant an amount equal to the product of (a) the excess of the per share fair market value of our common stock on the date of exercise over the strike price, multiplied by (b) the number of shares of common stock with respect to which the stock appreciation right is exercised. A stock appreciation right granted under the 2014 Plan vests at the rate specified in the stock appreciation right agreement as determined by the plan administrator.

The plan administrator determines the term of stock appreciation rights granted under the 2014 Plan, up to a maximum of ten years. Unless the terms of a participant s stock appreciation right agreement provides otherwise, if a participant s

service relationship with us, or any of our affiliates, ceases for any reason other than a termination for cause or a termination because of disability or death, the participant may exercise the vested portion of any stock appreciation right for a period of three months following the cessation of service. If a

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participant s service relationship with us, or any of our affiliates, ceases due to disability or death or the participant dies within a specified period following cessation of service, the participant or a beneficiary may exercise the vested portion of any stock appreciation right for a period of 12 months in the event of disability and 18 months in the event of death. In the event of a termination of participant s service for cause, the stock appreciation right will terminate upon the participant s cessation of service and the participant may not exercise the stock appreciation right following such termination. The term of the stock appreciation right may be further extended in the event that exercise of the stock appreciation right following termination of service is prohibited by applicable securities laws, or the sale of any common stock received upon exercise of the stock appreciation right would violate our insider trading policy. In no event, however, may a stock appreciation right be exercised beyond the expiration of its term.

Performance Awards. The 2014 Plan permits the grant of performance-based stock and cash awards that may qualify as performance-based compensation that is not subject to the $1 million limitation on the income tax deductibility of compensation paid per covered executive officer imposed by Section 162(m) of the Code. To assure that the compensation attributable to performance-based awards will so qualify, our compensation committee can structure such awards so that the stock or cash will be issued or paid pursuant to such award only following the achievement of certain pre-established performance goals during a designated performance period.

The criteria that the compensation committee may select to establish the performance goals include one or more of the following: (1) earnings (including earnings per share and net earnings); (2) earnings before interest, taxes and depreciation; (3) earnings before interest, taxes, depreciation and amortization; (4) earnings before interest, taxes, depreciation, amortization and legal settlements; (5) earnings before interest, taxes, depreciation, amortization, legal settlements and other income (expense); (6) earnings before interest, taxes, depreciation, amortization, legal settlements, other income (expense) and stock-based compensation; (7) earnings before interest, taxes, depreciation, amortization, legal settlements, other income (expense), stock-based compensation and changes in deferred revenue; (8) total stockholder return; (9) return on equity or average stockholder s equity; (10) return on assets, investment, or capital employed; (11) stock price; (12) margin (including gross margin); (13) income (before or after taxes); (14) operating income; (15) operating income after taxes; (16) pre-tax profit; (17) operating cash flow; (18) sales or revenue targets; (19) increases in revenue or product revenue; (20) expenses and cost reduction goals; (21) improvement in or attainment of working capital levels; (22) economic value added (or an equivalent metric); (23) market share; (24) cash flow; (25) cash flow per share; (26) share price performance; (27) debt reduction; (28) implementation or completion of projects or processes; (29) user satisfaction; (30) stockholders equity; (31) capital expenditures; (32) debt levels; (33) operating profit or net operating profit; (34) workforce diversity; (35) growth of net income or operating income; (36) billings; (37) bookings; (38) the number of users, including but not limited to unique users; (39) employee retention; (40) initiation of phases of clinical trials and/or studies by specified dates; (41) patient enrollment rates, (42) budget management; (43) submission to, or approval by, a regulatory body (including, but not limited to the FDA) with respect to products, studies and/or trials; and (44) to the extent that an Award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by the board of directors or our compensation committee.

The compensation committee may establish performance goals on a company-wide basis, with respect to one or more business units, divisions, affiliates or business segments, and in either absolute terms or relative to the performance of one or more comparable companies or the performance of one or more relevant indices. Unless specified otherwise (i) in the award agreement at the time the award is granted or (ii) in such other document setting forth the performance goals at the time the performance goals are established, the compensation committee will appropriately make adjustments in the method of calculating the attainment of performance goals for a performance period as follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects; (3) to exclude the effects of changes to generally accepted accounting principles; (4) to exclude the effects of any statutory adjustments to corporate tax rates; (5) to exclude the effects of any extraordinary items as determined under generally accepted

accounting principles; (6) to exclude the dilutive effects of acquisitions or joint ventures; (7) to assume that any business divested by the company achieved

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performance objectives at targeted levels during the balance of a performance period following such divestiture; (8) to exclude the effect of any change in the outstanding shares of common stock of the company by reason of any stock dividend or split, stock repurchase, reorganization, recapitalization, merger, consolidation, spin-off, combination or exchange of shares or other similar corporate change, or any distributions to common stockholders other than regular cash dividends; (9) to exclude the effects of stock based compensation and the award of bonuses under the company s bonus plans; (10) to exclude costs incurred in connection with potential acquisitions or divestitures that are required to be expensed under generally accepted accounting principles; (11) to exclude the goodwill and intangible asset impairment charges that are required to be recorded under generally accepted accounting principles, (12) to exclude the effects of the timing of acceptance for review and/or approval of submissions to the FDA or any other regulatory body and (13) to exclude the effect of any other unusual, non-recurring gain or loss or other extraordinary item.

Other Stock Awards. The plan administrator may grant other awards based in whole or in part by reference to our common stock. The plan administrator will set the number of shares under the award and all other terms and conditions of such awards.

Adjustment Provisions. In the event that there is a specified type of change in our capital structure, such as a stock split or recapitalization, the plan administrator will make appropriate adjustments to the class and maximum number of shares of our common stock subject to the 2014 Plan, the class and maximum number of shares of our common stock that may be issued upon the exercise of incentive stock options, the class and maximum number of shares of our common stock subject to stock awards that can be granted in a calendar year (as established under the 2014 Plan pursuant to Section 162(m) of the Code), and the class, number of shares and price per share of common stock subject to outstanding stock awards.

Corporate Transactions. In the event of certain specified significant corporate transactions, the plan administrator may take any one or more of the following actions as to outstanding awards, or as to a portion of any outstanding award under the 2014 Plan:

arrange for the assumption, continuation or substitution of a stock award by a surviving or acquiring entity or parent company;

arrange for the assignment of any reacquisition or repurchase rights held by us to the surviving or acquiring entity or parent company;

accelerate the vesting of the stock award and provide for its termination prior to the effective time of the corporate transaction;

arrange for the lapse of any reacquisition or repurchase rights held by us with respect to the stock award;

cancel or arrange for the cancellation of the stock award in exchange for such cash consideration, if any, as our plan administrator may deem appropriate; or

make a payment equal to the excess, if any, of the value of the property the participant would have received upon exercise of the stock award over the exercise price otherwise payable by the participant in connection with the exercise.

Changes in Control. The plan administrator may provide, in an individual award agreement, that the stock award will be subject to additional acceleration of vesting and exercisability in the event of a certain specified change in control. However, in the absence of such a provision, no such acceleration of the stock award will occur.

2004 Stock Incentive Plan

Our board of directors adopted, and our stockholders subsequently approved, the Cara Therapeutics 2004 Stock Incentive Plan, or the 2004 Plan, in September 2004. The 2004 Plan provides for the grant to our officers, directors, employees, consultants and advisors of incentive and nonqualified stock options to purchase our common stock, and also provides for the outright issuance of our common stock through restricted share awards.

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As of December 31 2013, options to purchase 490,160 shares of common stock were outstanding under the 2004 Plan, with a weighted average exercise price per share of $1.34. Although as of December 31 2013, 757,799 shares remained available for future issuance pursuant to the grant of options or restricted share awards under the 2004 Plan, upon effectiveness of the 2014 Plan in January 2014, we will not issue any further awards under the 2004 Plan.

Administration. The 2004 Plan may be administered either by our board of directors or a committee thereof that has been specifically designated by our board of directors to administer the 2004 Plan. The 2004 Plan is administered by our compensation committee.

Stock Options. Options granted under the 2004 Plan are evidenced by stock option agreements, containing such provisions as our board of directors deems advisable. All options granted under the 2004 Plan expire not more than ten years after the date of the grant and have an exercise price that is determined by our board of directors. Options under the 2004 Plan typically vest over a four-year period as follows: 25% of the shares underlying the option vest on the first anniversary of the date of the grant, and the remainder of the shares underlying the option vest in equal monthly installments over the 36 months thereafter.

Options granted under the 2004 Plan may not be assigned or transferred other than by will or the laws of descent or distribution. Unless otherwise provided in an optionee s stock option agreement, in the case of an optionee who is our employee on the date of grant of the options: (1) in the event of an optionee s termination of employment by reason of death or disability, the unvested portion of the option will terminate immediately and the vested portion of the option will terminate one year following such termination of employment in the case of death, and six months after such termination of employment in the case of disability (but will not continue to vest during such one-year or six-month period); and (2) in the event of an optionee s termination of employment for any other reason, the unvested portion of the option will terminate immediately and the vested portion of the option will terminate three months after such termination of employment.

Corporate Transactions. If we are a party to a merger or consolidation, or another transaction providing for the sale of all or substantially all of our stock or assets, the options will be subject to the terms of the agreement of merger, consolidation or sale, which may provide for any one or more of the following actions with respect to outstanding stock options, without the optionee s consent:

provide for the continuation or assumption of options, or provide for substitution of a substantially equivalent stock option, by the acquiring or succeeding entity;

provide that the option shall become immediately exercisable and will then terminate upon the consummation of the transaction unless exercised before that time; or

provide for a cash payment to the optionee for the full value of the options (whether or not then exercisable).

Termination or Amendment. Our board of directors may amend or terminate the 2004 Plan at any time, subject to certain restrictions. Our board of directors may modify or cancel an outstanding option in return for the grant of a new option covering the same or a different number of shares and the same or a different exercise price. However, no such amendment of the 2004 Plan or an option may materially adversely affect the rights of a participant in any option previously granted without the optionee s written consent.

Non-Employee Director Compensation

Prior to our initial public offering, we did not historically pay cash retainers or other compensation with respect to service on our board of directors, except for reimbursement of direct expenses incurred in connection with attending meetings of the board or committees. In addition, none of our non-employee directors held any stock options as of December 31, 2013.

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None of our non-employee directors received compensation for service on our board of directors during the year ended December 31, 2013 and, accordingly, we have not included a 2013 Director Compensation Table. Dr. Chalmers, our Chief Executive Officer, is also a director but does not receive any additional compensation for his service as a director. Dr. Chalmers compensation as an executive officer is set forth below under Executive Compensation 2013 Summary Compensation Table.

In January 2014, our board of directors approved a non-employee director compensation policy which became effective upon the completion of our initial public offering.

Under our director compensation policy, we will pay each of our non-employee directors a cash retainer for service on our board of directors and for service on each committee on which the director is a member, as set forth below. These retainers are payable in arrears in four equal quarterly installments on the last day of each quarter, provided that the amount of such payment will be prorated for any portion of such quarter that the director is not serving on our board of directors. No retainers will be paid in respect of any period prior to the completion of our initial public offering. The retainers paid to non-employee directors for service on our board of directors and for service on each committee of our board of directors on which the director is a member are as follows:

	Member Annual Service Retainer	Chairman Additional Annual Service Retainer
Board of Directors	$ 35,000	$ 25,000
Audit Committee	$ 6,500	$ 6,500
Compensation Committee	$ 5,000	$ 5,000
Nominating and Corporate Governance Committee	$ 3,500	$ 3,500

We also reimburse our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending our board of director and committee meetings. In addition, under our director compensation policy, each non-employee director serving on our board of directors at the time of our initial public offering and each non-employee director elected to our board of directors after the completion of our initial public offering will receive an option to purchase 20,000 shares of our common stock, or the initial option. With respect to each non-employee director serving on our board of directors at the time of our initial public offering, the exercise price of the initial options was $11.00 per share, which was the initial public offering price per share in our initial public offering. With respect to each non-employee director elected to our board of directors in the future, the exercise price of the initial option will be equal to the fair market value of our common stock on the date of grant. For our current non-employee directors, the initial option will vest concurrently with the expiration of the initial term of office for the class in which such director serves, subject to the director s continued service as a director. Further, on the date of each annual meeting of stockholders held after the completion of our initial public offering, each non-employee director that continues to serve as a non-employee member on our board of directors will receive an option to purchase 10,000 shares of our common stock. The exercise price of these options will be equal to the fair market value of our common stock on the date of grant, and the option will vest on the one year anniversary of the date of grant, subject to the director s continued service as a director.

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

401(k) Plan

We maintain the Cara Therapeutics Savings and Retirement Plan 401(k), or the 401(k) Plan, a tax-qualified retirement plan that provides eligible U.S. employees with an opportunity to save for retirement on a tax advantaged basis. Eligible employees are able to defer eligible compensation subject to applicable annual Internal Revenue Code limits. Pre-tax contributions are allocated to each participant s individual account and are then invested in selected investment alternatives according to the participant s directions. Contributions that we may make are subject to a vesting schedule; employees are immediately and fully vested in their contributions.

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The 401(k) Plan is intended to qualify under Sections 401(a) and 501(a) of the Code. As a tax-qualified retirement plan, contributions to the 401(k) Plan and earnings on those contributions are not taxable to the employees until distributed from the 401(k) Plan and all contributions are deductible by us when made.

Limitation of Liability and Indemnification

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

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

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

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

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

indemnification provisions.

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

Compensation Committee Interlocks and Insider Participation

None of our directors who currently serve as members of our compensation committee is, or has at any time during the past year been, one of our officers or employees. None of our executive officers currently serves, or in the past year has served, as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving on our board of directors or compensation committee.

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

The following table sets forth information as of February 28, 2014 about the number of shares of common stock and the percentage of common stock beneficially owned by:

- each of our directors and named executive officers;
- all of our directors and executive officers as a group; and
- each person, or any affiliated persons, who is a beneficial owner of more than 5% of our capital stock.

Ownership information is based upon information furnished by the respective individuals or entities, as the case may be.

We have determined beneficial ownership in accordance with the rules of the SEC. Except as indicated by the footnotes below, we believe, based on the information furnished to us, that the persons and entities named in the table below have sole voting and investment power with respect to all shares of common stock that they beneficially own, subject to applicable community property laws.

Applicable percentage ownership is based on 22,592,414 shares of common stock outstanding on February 28, 2014. In computing the number of shares of common stock beneficially owned by a person and the percentage ownership of that person, we have deemed outstanding shares of common stock to be subject to options held by that person that are currently exercisable or exercisable within 60 days after February 28, 2014. We have not deemed these shares outstanding, however, for the purpose of computing the percentage ownership of any other person.

Except as otherwise noted below, the address for each person or entity listed in the table is c/o Cara Therapeutics, Inc., 1 Parrott Drive, Shelton, Connecticut 06484.

Name of beneficial owner	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
5% stockholders:		
Esperante AB[(1)]	1,547,149	6.8%
Ascent Biomedical Ventures[(2)]	1,699,054	7.5%
Alta BioPharma Partners[(3)]	1,914,419	8.5%
MVM International Life Sciences No. 1 L.P.[(4)]	1,634,482	7.2%
Devon Park Bioventures L.P.[(5)]	1,576,404	7.0%
Rho Ventures VI, L.P.[(6)]	2,668,057	11.8%
Directors and named executive officers:		
Derek Chalmers, Ph.D.[(7)]	1,139,792	5.0%
James B. Jones, M.D., PharmD, FACEP[(8)]	93,800	*%

Frédérique Menzaghi, Ph.D.[9]	245,000	1.1%
Josef Schoell[10]	70,458	*%
Ed Hurwitz[3]	1,914,419	8.5%
Charles Moller, Ph.D.[5]	1,576,404	7.0%
Dean Slagel[1]	1,547,149	6.8%
Martin Vogelbaum[6]		*%
All current executive officers and directors as a group (8 persons)[11]	6,859,044	30.1%

* Represents beneficial ownership of less than one percent.

(1) Dean Slagel, a director of the company and Managing Director of Esperante AB, holds voting and/or dispositive power over the shares held by Esperante AB. The principal address for Esperante AB is PO Box 30127, SE-20061 Limhamn, Sweden.

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(2) Consists of (i) 963,896 shares held of record by Ascent Biomedical Ventures I, L.P., (ii) 130,730 shares held of record by Ascent Biomedical Ventures I Annex, L.P. and (iii) 604,428 shares held of record by Ascent Biomedical Ventures I NY, L.P. ABV, LLC is the general partner of Ascent Biomedical Ventures I, L.P., Ascent Biomedical Ventures I Annex, L.P. and Ascent Biomedical Ventures I NY, L.P. The directors of ABV, LLC, Geoffrey W. Smith and Steve Hochberg exercise sole dispositive and voting power over the shares owned by Ascent Biomedical Ventures I, L.P., Ascent Biomedical Ventures I Annex, L.P. and Ascent Biomedical Ventures I NY, L.P. The principal address for the entities affiliated with Ascent Biomedical Ventures is 142 West 57th Street, 4A, New York, NY 10019.

(3) Consists of (i) 1,753,447 shares held of record by Alta Biopharma Partners III, L.P. (ABP III), (ii) 117,760 shares held of record by Alta BioPharma Partners III GmbH & Co. Beteiligings KG (ABP III KG) and (iii) 43,212 shares held of record by Alta Embarcadero Biopharma Partners III, LLC AEPB III and, collectively, the Alta Funds). Alta BioPharma Management III, LLC (ABM III) is the general partner of ABP III and the managing limited partner of ABP III KG. Edward Hurwitz, one of our directors, Farah Champsi and Edward Penhoet are directors of ABM III, and the managers of AEBP III and may be deemed to share dispositive and voting power over the shares held by the Alta Funds. The principal address of the Alta Funds is One Embarcadero Center, 37th Floor, San Francisco, CA 94111.

(4) Consists of 1,618,137 shares held of record by MVM International Life Sciences No. 1 L.P. and 16,345 shares held of record by MVM Executive Limited. MVM International Life Sciences No. 1 L.P. and MVM Executive Limited are managed by MVM Life Sciences Partners LLP (MVM), an English Limited Liability Partnership. The individuals with shared voting power over MVM are Stephen Reeders, Eric Bednarski and Thomas Casdagli in respect of the shares held by MVM International Life Sciences No. 1 L.P. and MVM Executive Limited. The address for MVM and its affiliated entities is 6 Henrietta Street, London WC2E 8PU.

(5) The shares directly held by Devon Park Bioventures, L.P. (Dev LP) are indirectly held by Devon Park Associates, L.P. (Dev GP), as general partner of Dev LP, Devon Park Associates, LLC (Dev LLC), as general partner of Dev GP, and each of the individual managing members of Dev LLC. The individual managing members (collectively, the Dev Managers) of Dev LLC are Charles Moller, Ph.D, Marc Ostro, Ph.D, and Devang Kantesaria, M.D. Dev GP, Dev LLC, and the Dev Managers may share voting and dispositive power over the shares directly held by Dev LP. The principal address for the entities affiliated with the Dev GP is 1400 Liberty Ridge Drive, Suite 103, Wayne, PA 19087.

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

(7) Consists of 1,099,792 shares held directly by Dr. Chalmers and 40,000 shares of common stock underlying options that are vested and exercisable within 60 days of February 28, 2014.

(8) Consists of 93,800 shares of common stock underlying options that are vested and exercisable within 60 days of February 28, 2014.

(9) Consists of 160,000 shares held directly by Dr. Menzaghi and 85,000 shares of common stock underlying options that are vested and exercisable within 60 days of February 28, 2014.

(10) Consists of 70,458 shares of common stock underlying options that are vested and exercisable within 60 days of February 28, 2014.

(11) Consists of the shares listed in footnotes (1), (3), (5), (7), (9) and (10). Also includes 365,822 shares held directly by Michael E. Lewis, Ph.D., our Chief Scientific Advisor.

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Securities Authorized for Issuance Under Equity Compensation Plans.

The following table sets forth information as of December 31, 2013 regarding compensation plans under which equity securities of the Company are authorized for issuance:

Plan category	Number of securities to be issued upon exercise of outstanding options, warrants and rights (a)	Weighted-average exercise price of outstanding options, warrants and rights (b)	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column[a]) (c)
Equity compensation plans approved by security holders[a]	490,160	$ 1.34	757,799[b]
Equity compensation plans not approved by security holders			
Total	490,160	$ 1.34	757,799

(a) Relates to our 2004 Plan.

(b) Although as of December 31 2013, 757,799 shares remained available for future issuance pursuant to the grant of options or restricted share awards under the 2004 Plan, upon effectiveness of the 2014 Plan in January 2014, we ceased issuing awards under the 2004 Plan.

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

Other than compensation arrangements, we describe below transactions and series of similar transactions, since January 1, 2011, to which we were a party or will be a party, in which:

the amounts involved exceeded or will exceed $120 thousand and

any of our directors, executive officers, or holders of more than 5% of our capital stock, or any member of the immediate family of the foregoing persons, had or will have a direct or indirect material interest.

Compensation arrangements for our named executive officers are described in Item 11, Executive Compensation of this Annual Report on Form 10-K.

Participation in Initial Public Offering

Certain of our existing principal stockholders, Ascent Biomedical Ventures, Alta BioPharma Partners and Rho Ventures VI, L.P. and their affiliated entities purchased an aggregate of approximately $4.0 million in shares of our common stock in our initial public offering at the initial public offering price. Ascent Biomedical Ventures, a stockholder who holds more than 5% of our capital stock, purchased 25,000 shares, amounting to $275,000. Alta BioPharma Partners, a stockholder who holds more than 5% of our capital stock and is an entity with which one of our directors, Ed Hurwitz, is affiliated with, purchased 112,817 shares, amounting to $1,240,987. Rho Ventures VI, L.P., a stockholder who holds more than 5% of our capital stock and is an entity with which one of our directors, Martin Vogelbaum, is a non-managing member, purchased 225,818 shares, amounting to $2,483,998.

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2012 Bridge Financing

In October and December 2012, we issued unsecured demand promissory notes in an aggregate principal amount of approximately $1.0 million, or the 2012 Bridge Financing. The participants in the 2012 Bridge Financing included certain beneficial owners of more than 5% of our capital stock and entities affiliated with certain of our directors, as set forth in the table below:

Participants	Principal Amount
Ascent Biomedical Ventures and its affiliates(1)	$ 212,208
Alta BioPharma Partners and its affiliates(2)	$ 228,377
Devon Park Bioventures L.P.(3)	$ 199,830
Rho Ventures VI, L.P.(4)	$ 309,585

(1) These promissory notes were purchased by Ascent Biomedical Ventures I Annex, L.P. and Ascent Biomedical Ventures I NY, LP.

(2) These promissory notes were purchased by Alta BioPharma Partners III, L.P., Alta BioPharma Partners III GmbH & Co. Beteiligungs KG and Alta Embarcadero BioPharma Partners III, LLC. Alta BioPharma Partners III, L.P., Alta BioPharma Partners III GmbH & Co. Beteiligings KG and Alta Embarcadero BioPharma Partners III, LLC are collectively referred to as the Alta Funds. Alta BioPharma Management Partners III, LLC is the general partner of Alta BioPharma Partners III, L.P. and the managing limited partner of Alta BioPharma Partners III GmbH & Co. Beteiligungs KG. Edward Hurwitz, one of our directors, is a director of Alta BioPharma Management Partners III, LLC and manager of Alta Embarcadero BioPharma Partners III, LLC.

(3) Charles Moller, Ph.D., one of our directors, is a managing member of Devon Park Associates, LLC, the general partner of Devon Park Associates, L.P. Devon Park Associates, L.P. is the general partner of Devon Park Bioventures, L.P.

(4) Martin Vogelbaum, one of our directors, is a non-managing member of RMV VI, L.L.C., the general partner of Rho Ventures VI, L.P.

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2013 Bridge Financing

In December 2012 and February 2013, we issued an aggregate of $4.0 million principal amount of convertible promissory notes due August 28, 2013, or the 2013 Bridge Financing. 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 would have resulted in the automatic conversion of the notes into shares of a newly issued class of equity securities in the event of a qualifying financing prior to maturity. The mandatory conversion did not occur and, upon maturity, note holders elected to convert the aggregate amount of $3.9 million in principal plus accrued interest into 2,692,291 shares of Series D Preferred Stock. We repaid the remaining notes upon maturity in the aggregate amount of approximately $300 thousand in principal and accrued interest. The participants in the 2013 Bridge Financing included certain executive officers, beneficial owners of more than 5% of our capital stock and entities affiliated with certain of our directors, as set forth in the table below:

Participants	Principal Amount	Shares of Series D Preferred Stock Received on Conversion of Notes
Esperante AB[1]	$ 288,467	210,373
Ascent Biomedical Ventures and its affiliates[2]	$ 533,216	388,221
Alta BioPharma Partners and its affiliates[3]	$ 573,843	417,799
MVM International Life Sciences No. 1 L.P. and its affiliates[4]	$ 250,000	
Healthcare Private Equity Limited Partnership[5]	$ 250,217	180,997
Devon Park Bioventures L.P.[6]	$ 502,113	365,576
Rho Ventures VI, L.P.[7]	$ 777,896	566,368
Derek Chalmers[8]	$ 181,833	132,607
Frédérique Menzaghi[9]	$ 28,688	
Michael E. Lewis[10]	$ 12,247	8,931

(1) Dean Slagel, one of our directors, is Managing Director of Esperante AB.

(2) These promissory notes were purchased by Ascent Biomedical Ventures I Annex, L.P. and Ascent Biomedical Ventures I NY, L.P. The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2012 Bridge Financing and 2013 Bridge Financing.

(3) These promissory notes were purchased by Alta BioPharma Partners III, L.P., Alta BioPharma Partners III GmbH & Co. Beteiligungs KG and Alta Embarcadero BioPharma Partners III, LLC. Alta BioPharma Partners III, L.P., Alta BioPharma Partners III GmbH & Co. Beteiligings KG and Alta Embarcadero BioPharma Partners III, LLC are collectively referred to as the Alta Funds. Alta BioPharma Management Partners III, LLC is the general partner of Alta BioPharma Partners III, L.P. and the managing limited partner of Alta BioPharma Partners III GmbH & Co. Beteiligungs KG. Edward Hurwitz, one of our directors, is a director of Alta BioPharma Management Partners III, LLC and manager of Alta Embarcadero BioPharma Partners III, LLC. The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2012 Bridge Financing and 2013 Bridge Financing.

(4) These promissory notes were purchased by MVM International Life Sciences No. 1 LP and MVM Executive Limited. MVM International Life Sciences No. 1 L.P. and MVM Executive Limited are managed by MVM Life Sciences Partners LLP, an English Limited Liability Partnership. Dr. Stephen Reeders, one of our former directors, was associated with MVM Life Sciences Partners LLP at the time of the 2013 Bridge Financing. Principal under these notes and accrued interest was repaid in September 2013.

(5) Healthcare Private Equity Limited Partnership was previously the beneficial owner of greater than 5% of our capital stock.

(6) Charles Moller, Ph.D., one of our directors, is a managing member of Devon Park Associates, LLC, the general partner of Devon Park Associates, L.P. Devon Park Associates, L.P. is the general partner of Devon

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Park Bioventures, L.P. The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2012 Bridge Financing and 2013 Bridge Financing.

(7) Martin Vogelbaum, one of our directors, is a non-managing member of RMV VI, LLC, the general partner of Rho Ventures VI, L.P. The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2012 Bridge Financing and 2013 Bridge Financing.

(8) The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2013 Bridge Financing.

(9) Principal under this note and accrued interest was repaid in September 2013.

(10) The shares of Series D Preferred Stock received upon conversion of notes described above includes the conversion of the principal and accrued interest on notes issued in the 2013 Bridge Financial.

Consulting Arrangement with Michael Lewis

Michael E. Lewis, Ph.D, one of our founders and our Chief Scientific Advisor, has historically provided services to us through BioDiligence Partners, Inc., or BDP. BDP is a consulting firm that is wholly owned by Mr. Lewis and members of his immediate family and of which Mr. Lewis and his wife are the only employees. Under the terms of a Services Agreement between with BDP, as amended, we pay BDP $99 thousand per year, plus 70% of the documented cost of BDP s health insurance plan. In return, Mr. Lewis devotes 70% of his professional efforts to us. We made total payments to BDP of approximately $134 thousand for the year ended December 31, 2013.

Policies and Procedures for Related Party Transactions

Our board of directors has adopted a written related person transaction policy to set forth the policies and procedures for the review and approval or ratification of related person transactions. This policy covers any transaction, arrangement or relationship, or any series of similar transactions, arrangements or relationships in which we were or are to be a participant, the amount involved exceeds $120 thousand and a related person had or will have a direct or indirect material interest, including, without limitation, purchases of goods or services by or from the related person or entities in which the related person has a material interest, indebtedness, guarantees of indebtedness or employment by us of a related person.

Director Independence

Under the listing requirements and rules of The NASDAQ Global Market, independent directors must comprise a majority of a listed company s board of directors within a specified period of time after our initial public offering.

Our board of directors has undertaken a review of its composition, the composition of its committees, and the independence of each director. Based upon information requested from and provided by each director concerning his or her background, employment, and affiliations, including family relationships, our board of directors has determined that each of our directors, except Dr. Chalmers, are independent as that term is defined under the applicable rules and regulations of the Securities and Exchange Commission, or the SEC, and the listing requirements and rules of The NASDAQ Global Market. In making this determination, our board of directors considered the current and prior relationships that each non-employee director has with our company and all other facts and circumstances our board of directors deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director.

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

The following table presents fees for professional services provided by Ernst & Young LLP for the years ended December 31, 2012 and 2013 (amounts in thousands):

	Year Ended December 31,	
	2012	2013
Audit fees	$ 64	$ 1,383[(a)]
Audit-related fees		
Tax fees		
All other fees		
Total	$ 64	$ 1,383

(a) Audit fees consist of the aggregate fees billed for professional services rendered for (i) the audit of our annual financial statements; (ii) the filing of our Registration Statement on Form S-1 related to our initial public offering; and (iii) accounting consultations.

Consistent with SEC policies regarding auditor independence and the audit committee s charter, the audit committee has responsibility for engaging, setting compensation for and reviewing the performance of the independent registered public accounting firm.

Prior to our initial public offering in January 2014, we had not constituted an audit committee of the board of directors. However, the board of directors as a whole approved all of the professional services provided by Ernst & Young LLP for the years ended December 31, 2012 and 2013.

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PART IV

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

All schedules for which provision is made in the applicable accounting regulations of the SEC which are not included with this additional financial data have been omitted because they are not applicable or the required information is shown in the Financial Statements or Notes thereto.

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.
4.2[(4)]	Warrant to purchase shares of Common Stock issued to Connecticut Innovations, Inc., dated September 25, 2007.
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.

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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.
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).

+ Indicates management contract or compensatory plan.
* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.
filed herewith
(1) Filed as exhibit 3.1 to the Registrant s Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.
(2) Filed as exhibit 3.2 to the Registrant s Current Report on Form 8-K (File No. 001-36279) filed with the Securities and Exchange Commission on February 7, 2014 and incorporated herein by reference.
(3) Filed as an exhibit (having the same exhibit number) to Pre-effective Amendment No. 2 to the Registrant s Registration Statement on Form S-1 Registration No. 333-192230) filed with the Securities and Exchange Commission on November 8, 2013 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.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on this 27th day of March 2014.

CARA THERAPEUTICS, INC.

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

Signature	Title	Date
/s/ DEREK CHALMERS Derek Chalmers, Ph.D.	President, Chief Executive Officer and Director (*Principal Executive Officer)*	March 27, 2014
/s/ JOSEF SCHOELL Josef Schoell	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 27, 2014
/s/ ED HURWITZ Ed Hurwitz	Director	March 27, 2014
/s/ CHARLES MOLLER Charles Moller, Ph.D.	Director	March 27, 2014
/s/ DEAN SLAGEL Dean Slagel	Director	March 27, 2014
/s/ MARTIN VOGELBAUM Martin Vogelbaum	Director	March 27, 2014

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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, 2013 and 2012, and the related statements of operations, convertible preferred stock and stockholders (deficit) equity and cash flows for each of the three years in the period ended December 31, 2013. 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, 2013 and 2012, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2013, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 27, 2014

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CARA THERAPEUTICS, INC.

BALANCE SHEETS

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

	December 31, 2012	December 31, 2013
Assets		
Current assets:		
Cash and cash equivalents	$ 1,117	$ 12,357
Income tax receivable	31	61
Prepaid expenses & other current assets	80	2,140
Total current assets	1,228	14,558
Property and equipment, net	3,609	2,825
Restricted cash	700	700
Total assets	$ 5,537	$ 18,083
Liabilities, convertible preferred stock and stockholders (deficit) equity		
Current liabilities:		
Current installment of long-term debt	$ 307	$
Convertible promissory notes	473	
Accounts payable and accrued expenses	906	1,958
Deferred Revenue		3,475
Total current liabilities	1,686	5,433
Deferred lease obligation	1,377	1,139
Liability under license agreement	35	
Commitments and contingencies *(Note 19)*		
Convertible Preferred stock; $0.001 par value; 26,636,118 shares at December 31, 2012 and 29,402,200 shares at December 31, 2013 authorized, 26,636,118 shares at December 31, 2012, and 29,186,929 shares at December 31, 2013 issued and outstanding, respectively; aggregate liquidation preference of $58,530 at December 31, 2012 and $65,969 at December 31, 2013 respectively	58,522	65,586
Beneficial conversion feature on Convertible Promissory Notes	2,050	
Stockholders (deficit) equity:		
Common stock; $.001 par value; 43,000,000 shares authorized at December 31, 2012 and 50,000,000 shares authorized at December 31, 2013, 3,328,698, and 4,288,243 shares issued and outstanding at December 31, 2012 and 2013, respectively	3	4
Additional paid-in capital	1,248	8,377
Accumulated deficit	(59,384)	(62,456)
Total stockholders (deficit) equity	(58,133)	(54,075)

Total liabilities, convertible preferred stock and stockholders (deficit) equity	$ 5,537	$ 18,083

See Notes to Financial Statements.

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CARA THERAPEUTICS, INC.

STATEMENTS OF OPERATIONS

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

	Year Ended December 31,		
	2011	**2012**	**2013**
Revenue:			
License and milestone fees	$	$ 1,190	$ 9,637
Collaborative revenue			2,327
Total revenue		1,190	11,964
Operating expenses:			
Research and development	7,159	4,597	8,685
General and administrative	2,407	2,829	3,516
Total operating expenses	9,566	7,426	12,201
Operating loss	(9,566)	(6,236)	(237)
Interest expense, net	(95)	(66)	(3,756)
Other expense	(180)		
Loss before benefit from income taxes	(9,841)	(6,302)	(3,993)
Benefit from income taxes	35	31	30
Net loss	$ (9,806)	$ (6,271)	$ (3,963)
Net loss available to common stockholders:			
Basic and Diluted	$ (9,806)	$ (6,271)	$ (3,072)
Loss per share available to common stockholders:			
Basic and Diluted	$ (3.03)	$ (1.90)	$ (0.74)
Weighted average shares:			
Basic and Diluted	3,235,743	3,299,993	4,133,138

See Notes to Financial Statements.

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CARA THERAPEUTICS, INC.

STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS (DEFICIT) EQUITY

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

	Common Stock					Convertible Preferred Stock		Beneficial Conversion Feature on Convertible Promissory Notes
	Shares	Amount	Additional Paid-in Capital	Accumulated Deficit	Total Stockholders (Deficit) Equity	Shares	Amount	Amount
Balance at December 31, 2010	3,233,237	$ 3	949	$ (43,307)	$ (42,355)	19,538,469	$ 47,162	$
Issuance of Series D convertible preferred stock						6,924,038	11,006	
Stock-based compensation expense			95		95			
Stock option exercise	3,400		2		2			
Net loss				(9,806)	(9,806)			
Balance at December 31, 2011	3,236,637	3	1,046	(53,113)	(52,064)	26,462,507	58,168	
Issuance of Junior convertible preferred stock						173,611	354	
Issuance of common stock	58,061		86		86			
Beneficial conversion feature on convertible promissory notes								2,050
Stock-based compensation expense			61		61			
Stock option exercise	34,000		55		55			
Net loss				(6,271)	(6,271)			
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	$

See Notes to Financial Statements.

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CARA THERAPEUTICS, INC.

STATEMENTS OF CASH FLOWS

(in thousands)

	Year Ended December 31,		
	2011	**2012**	**2013**
Operating activities			
Net loss	$ (9,806)	$ (6,271)	$ (3,963)
Adjustments to reconcile net loss to net cash (used in) provided by operations:			
Non-cash compensation expense	95	61	123
Change in fair value of liability under license agreement	(20)	(25)	(35)
Change in fair value of Investor rights / obligation	179		
Accrued interest and amortization of beneficial conversion feature on promissory notes		25	3,605
Depreciation & amortization	1,170	1,021	789
Deferred rent costs	(191)	(214)	(238)
Amortization of financing costs	16	4	117
Loss/(gain) on sale of property and equipment	(9)	286	
Changes in operating assets and liabilities:			
Other receivables		18	
Income tax receivable	6	8	(30)
Prepaid expenses	(66)	73	(1,736)
Restricted cash	294	294	
Accounts payable and accrued expenses	1,487	(1,311)	722
Deferred revenue			3,475
Net cash (used in) provided by operating activities	(6,845)	(6,031)	2,829
Investing activities			
Purchases of property and equipment	(15)		(5)
Proceeds from sale of property and equipment	60	511	
Net cash provided by (used in) investing activities	45	511	(5)
Financing activities			
Proceeds from convertible promissory notes		2,538	1,462
Financing costs on convertible promissory notes		(47)	(70)
Repayment of convertible promissory notes			(311)
Repayment of long-term debt	(848)	(446)	(307)
Issuance of common stock		86	
Stock option exercise	2	55	
Proceeds from sale of Series D convertible preferred stock	9,982		
Proceeds from sale of Junior convertible preferred stock		354	
Proceeds from sale of Junior A convertible preferred stock			7,642

Net cash provided by financing activities	9,136	2,540	8,416
Net cash increase (decrease) for the period	2,336	(2,980)	11,240
Cash & cash equivalents at beginning of period	1,761	4,097	1,117
Cash & cash equivalents at end of period	$ 4,097	$ 1,117	$ 12,357
Supplemental disclosure of cash flow information			
Cash paid for income taxes			
Cash paid for interest	$ 85	$ 20	$ 37

See Notes to Financial Statements.

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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 by selectively targeting kappa opioid receptors.

The registration statement relating to the Company s initial public offering (IPO) was declared effective by the Securities and Exchange Commission on January 30, 2014. As a result of the IPO, the Company received net proceeds on February 5, 2014 of approximately $55,900 from the sale of 5,750,000 shares of common stock, after deducting approximately $7,400 of underwriting discounts and commissions and estimated offering expenses payable by the Company. Refer to Note 22, Subsequent Events.

Prior to the IPO, the Company has raised several rounds of equity financing and issued debt, resulting in aggregate net proceeds of approximately $73,309 through December 31, 2013. The Company has incurred substantial losses and negative cash flows from operations in nearly every fiscal period since inception, and expects operating losses and negative cash flows to continue into the foreseeable future. The accompanying financial statements have been prepared assuming the Company will continue to operate as a going concern, which contemplates the realization of assets and the settlement of liabilities and commitments in the normal course of business. In April 2013, the Company entered into a License Agreement and Stock Purchase Agreement with Maruishi Pharmaceutical Co., Ltd. (Maruishi), which collectively added $23,000 in cash (see Note 12). As of December 31, 2013, the Company has unrestricted cash and cash equivalents of $12,357 and an accumulated deficit of $62,456. The Company recognized net loss of $3,963, which included revenue from the Maruishi license, and had net cash flows provided by operations of $2,829 for the year ended December 31, 2013. The Company expects that cash and cash equivalents at December 31, 2013, together with the proceeds from its initial public offering, 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 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.

In prior years, the Company was a development stage company as defined by ASC 915 *Development Stage Entities*.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States (GAAP) requires management to make estimates, judgments and assumptions that affect the amounts reported in the financial statements and accompanying notes including collaborative revenue and clinical expenses during the period. Actual results and outcomes may differ materially from management s estimates, judgments and assumptions.

Fair Value Measurements

The Company s financial instruments consist of cash and cash equivalents, restricted cash, accounts payable, accrued liabilities, investor rights/obligations, liability under license agreement, long-term debt and contingent call option. Fair value estimates of these instruments are made at a specific point in time, based on

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relevant market information. These estimates may be subjective in nature and involve uncertainties and matters of significant judgment and therefore cannot be determined with precision. The carrying amount of cash and cash equivalents, restricted cash, accounts payable and accrued liabilities and debt are generally considered to be representative of their respective fair values because of the short-term nature of those instruments. The fair value of the Company s investor rights/obligation liability has been estimated utilizing the Company s own internal analysis, including variables for timing of the preferred stock tranches. The liability under license agreement has been valued based upon the Black-Scholes option valuation model and other probability estimates. The fair value of the Company s contingent call option was calculated by estimating the accreted value of the convertible promissory 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.

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 market assumptions and are classified into the following fair value hierarchy:

Level 1 Observable inputs quoted prices in active markets for identical assets and liabilities.

Level 2 Observable inputs other than the quoted prices in active markets for identical assets and liabilities such as quoted prices for similar instruments, quoted prices for identical or similar instruments in inactive markets, or other inputs that are observable or can be corroborated by observable market data.

Level 3 Unobservable inputs includes amounts derived from valuation models where one or more significant inputs are unobservable and require the company to develop relevant assumptions.

The following table summarizes the financial assets and liabilities measured at fair value on a recurring basis as of December 31, 2012 and 2013 and by level within the fair value hierarchy:

	Balance December 31, 2012	Level 1	Level 2	Level 3
Financial assets				

Cash equivalents:				
Money market funds	$ 1,117	$ 1,117	$	$
Restricted cash:				
Bank Certificate of Deposit	700	700		
Total	$ 1,817	$ 1,817	$	$
Financial liabilities				
Contingent call option *(Note 8)*	$ 41	$	$	$ 41
Liability under license agreement *(Note 15)*	35			35
Total	$ 76	$	$	$ 76

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	Balance December 31, 2013	Level 1	Level 2	Level 3
Financial assets				
Cash equivalents:				
Money market funds	$ 12,357	$ 12,357	$	$
Restricted cash:				
Bank Certificate of Deposit	700	700		
Total	$ 13,057	$ 13,057	$	$

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

	December 31, 2012	2013
Liabilities		
Balance at beginning of period	$ 60	$ 76
Amounts acquired or issued	41	
Net (gains) losses (realized and unrealized)	(25)	(76)
Net settlements		
Balance at end of period	$ 76	$

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less when purchased to be cash equivalents. The carrying amount of cash and cash equivalents approximates its fair value due to its short-term nature.

Concentration of Credit Risk

Financial instruments, which potentially subject the Company to significant concentration of credit risk, consist primarily of cash and cash equivalents. The Company 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.

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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	10 years

Long-Lived Assets

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

Common Stock Valuation

Due to the absence of an active market for the Company s common stock prior to its initial public offering, 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 at various reporting dates. Each valuation includes estimates and assumptions that require the Company s 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, and 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.

Revenue Recognition

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

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.

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

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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 consideration 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 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 that do not represent separate units of accounting are deferred. The Company has determined that its license deliverables represent separate units of accounting.

Arrangement consideration allocated to research and development services that represent separate units of accounting are 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.

The Company s license agreements have 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 milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone in accordance with ASC 605-28, *Revenue Recognition Milestone Method*. 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, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment.

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The Company generally considers non-refundable development and regulatory milestones that the Company expects to be achieved as a result of the Company s efforts during the period of the Company s performance obligations under the license and research agreements to be substantive and recognizes them as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If not considered to be substantive, the Company initially defers milestones and recognizes them over the remaining term of the Company s performance obligations. If no such performance obligation exist, milestones that are not considered substantive because the Company does not contribute effort to the achievement of such milestones 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 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. The capitalized amounts are expensed as the related goods are delivered or services are performed. As of December 31, 2012 and 2013, the Company recorded $0 and $262 as prepaid 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 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. There are no material uncertain tax positions taken as of December 31, 2012 and December 31, 2013. 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 and non-employees as compensation for services performed. Employee awards of stock-based compensation are accounted for in accordance with ASC 718, *Stock Compensation.* ASC 718 requires all share-based payments to employees, including grants of employee stock options, to be recognized in the statements of operations based on their grant date fair values. The grant date fair value of stock options is estimated using a Black-Scholes option valuation model. Prior to the effective date of

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the registration statement related to the Company s initial public offering, 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*. Subsequently, common stock prices are the closing price of the Company s common stock as quoted on The NASDAQ Global Market. See Note 13, *2004 Stock Incentive Plan* for the other inputs to the Black-Scholes model.

The Company applies a forfeiture rate to the number of unvested awards in each reporting period in order to estimate 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. 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 issued to non-employees under ASC 505, *Equity-Based Payments to Non-Employees.* As such, the fair value of such options is periodically re-measured and income or expense is recognized during their vesting terms. Compensation cost relating to awards with service-based graded vesting schedules is recognized using the straight-line method.

Earnings Per Share

The Company computes basic earnings (loss) per share using the two-class method, which includes the weighted-average number of common stock outstanding during the period and other securities that participate in dividends (a participating security). The Company s convertible preferred stock are participating securities as defined by ASC 260-10, Earnings per Share. Under the two-class method, basic net earnings (loss) per share applicable to common stockholders is computed by dividing the net earnings (loss) applicable to common stockholders by the weighted-average number of common shares outstanding for the period. Diluted net earnings (loss) per share is computed using the more dilutive of (1) the two-class method, or (2) the if-converted method. The Company allocates net earnings 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 earnings income (loss) per share gives effect to all potentially dilutive securities, including convertible preferred stock, convertible promissory notes and shares issuable upon the exercise of outstanding stock options and warrants, using the treasury stock method. For the years ended December 31, 2011, 2012 and 2013, the Company has excluded the effects of all potentially dilutive shares, which include convertible preferred stock, convertible promissory notes, warrants for common stock and common stock options, from the weighted-average number of common shares outstanding as their inclusion would be anti-dilutive due to the Company s net losses.

All calculations of earnings (loss) per share, both basic and diluted, reflect the 1-for-2.5 reverse stock split. Refer to Note 22, *Subsequent Events*. Refer to Note 16, *Loss per Share*, for the Company s calculations of earnings (loss) per share 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 in one operating segment: the discovery and development of novel therapeutics to treat pain.

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Leases

The Company recognizes rent expense for operating leases, where the amount of rental payments over the term of the lease is stated in the lease agreement, on a straight-line basis (including the effect of reduced or free rent and rent escalations) over the life of the lease beginning on the date the Company takes possession of the property. 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 used to determine whether a lease is 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 Operations.

Deferred Financing Costs

Deferred financing costs represent legal, other professional and bank underwriting fees incurred in connection with the issuance of debt. Such fees are amortized over the life of the related debt using the interest method. Amortization of deferred financing costs is included in interest expense, net.

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 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 are included in Accounts payable and accrued expenses in the Balance Sheets.

Reclassifications

Certain prior year legal costs within the Statement of Operations have been reclassified from Research and development to General and administrative to conform to current presentation.

3. Prepaid expenses and other current assets

As of December 31, 2012, prepaid expense and other current assets was $80, consisting of $31 of prepaid insurance and $49 of deferred financing costs. As of December 31, 2013, prepaid expense and other current assets was $2,140, consisting of $1,833 of IPO costs, $262 of R&D clinical costs, $34 of prepaid insurance, and $11 of other costs.

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4. Property and Equipment, Net

Property and equipment, net consists of the following:

	December 31,	
	2012	2013
Computer and office equipment	$ 270	$ 275
Laboratory equipment	233	233
Furniture and fixtures	153	153
Software	126	126
Leasehold improvements	7,453	7,453
	$ 8,235	$ 8,240
Less accumulated depreciation and amortization	4,626	5,415
Property and equipment, net	$ 3,609	$ 2,825

Depreciation and amortization expense included in research and development expense and general and administrative expense was $1,170, $1,021 and $789 for the years ended December 31, 2011, 2012 and 2013, respectively.

During the third quarter of 2012, the Company sold most of its laboratory equipment for net proceeds of $511 resulting in a net loss of $286, included in general and administrative expense.

5. Restricted Cash

The Company is required to maintain a stand-by letter of credit as security under the Shelton Lease (refer to Note 19). The Company s bank requires the Company to maintain a restricted cash balance equal to the stand-by letter of credit, which is invested in a bank certificate of deposit. Each March, the letter of credit amount was reduced by $294 until 2012, after which the letter of credit balance remains at $700 through the end of the lease term in 2017. As of December 31, 2012 and 2013, the Company has $700 of restricted cash in long-term assets.

6. Deferred Financing Costs

Deferred financing costs related to the convertible promissory notes as of December 31, 2012 and the CT Innovations term loan as of December 31, 2011 were included in prepaid expenses and other current assets (refer to Notes 8 and 9). Deferred financing costs are amortized over the life of the related debt using the effective interest method. For the years ended December 31, 2011, 2012 and 2013, deferred financing costs of $16, $4, and $117, respectively were amortized and included in interest expense.

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7. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	December 31,	
	2012	**2013**
Accounts payable	$ 472	$ 676
Accrued research projects	20	405
Accrued professional fees	108	739
Accrued compensation and benefits	48	83
Contingent call option *(Note 8)*	41	
Accrued other	217	55
	$ 906	$ 1,958

8. 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. In connection with these notes, the Company incurred $117 of financing costs which is included in prepaid expenses and other current assets (refer to Notes 3 and 6). 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 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 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.

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The mandatory conversion of the Notes would occur 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 automatically convert 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. As of December 28, 2012, the Company estimated the probability of an equity offering in excess of $10,000 closing before August 28, 2013 to be 15%. The Company classified the liability within Level 3 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. There was no change in the fair value of the contingent call option as of December 31, 2012. The estimated fair value of the contingent call option was reduced to zero, 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 Preferred Stock, and the remaining Notes, in the aggregate amount of $311 in principal and accrued interest, were repaid during October 2013. As of December 31, 2013, there were no Notes outstanding.

9. 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. In connection with this Loan, the Company incurred $149 of financing costs which were included in other assets and were being amortized as interest expense over the life of the Loan (refer to Note 6). The Loan was collateralized by property and equipment located in Shelton, Connecticut and owned as of December 31, 2007. As of December 31, 2012, the net carrying value of the property and equipment, including leasehold improvements, that served as collateral for the Loan was $3,593. 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%. Maintaining Connecticut presence is within management s control, and the

Company had no plans to relocate the majority of its operations; therefore, the classification of the Loan was based on the scheduled payment dates.

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 remaining principal balance of the Loan was $307 as of December 31, 2012, which was classified as current installment of long-term debt. The Company repaid all remaining amounts outstanding under the Loan, including accrued interest thereon, in April 2013.

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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 incorporates the non-financial covenants of the Loan described above. If the Company fails 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.

10. Convertible Preferred Stock

In June 2010, the Company authorized the issuance of up to 10,386,057 shares of Series D convertible preferred stock, $0.001 par value per share (Series D Preferred Stock) at a price per share of $1.444244. The financing was initially contemplated to take place in three tranches of $5,000 each. In July and August 2010, the Company issued 3,462,019 shares of Series D Preferred Stock in connection with the closing of the first tranche. In March 2011, the purchase agreement was amended to divide the second tranche into two separate closings of $3,000 and $2,000, respectively, and extend the date for the closing of the final tranche to August 2011. The two closings comprising the second tranche were completed in the amount of $3,000 in March 2011 and $2,000 in July 2011. The final tranche of $5,000 closed in August 2011.

The right and obligation on the part of the investors in the initial tranche of the Series D Preferred Stock financing to purchase additional shares of Series D Preferred Stock in the future tranches (the investor right/obligation) represents a free-standing financial instrument, which was recorded at its fair value as a liability on the date of the initial issuance of Series D Preferred Stock, July 19, 2010, and this liability was marked to market at each subsequent reporting date at which it remained outstanding in accordance with ASC 480, *Distinguishing Liabilities from Equity*. The fair value of the liability at July 19, 2010 was $733. The fair value at December 31, 2010 was $844. The fair value at December 31, 2011 was zero, because the investor right/obligation was no longer outstanding as it had been exercised in full upon the closing of the final tranche of the financing in August 2011. The change in fair value related to the investor right/obligation was approximately $179 during 2011 and approximately $111 during the period July 19, 2010 to December 31, 2010. The changes in fair value were recorded within other expense in the Statements of Operations.

In May 2012, the Company issued to Chong Kun Dang Pharmaceutical Corporation (CKD) 173,611 shares of Junior convertible preferred stock, $0.001 par value per share (Junior Preferred Stock) having an estimated fair value of $354. The shares were sold as part of the license transaction with CKD (refer to Note 12).

As of December 31, 2012, the Company was authorized to issue up to 26,636,118 shares of convertible preferred stock, $0.001 par value per share (consisting of 2,000,000 shares of Series A convertible preferred stock (Series A Preferred Stock), 2,370,000 shares of Series B convertible preferred stock (Series B Preferred Stock), 11,706,450 shares of Series C convertible preferred stock (Series C Preferred Stock), 10,386,057 shares of Series D Preferred Stock and 173,611 of Junior Preferred Stock, respectively).

In April 2013, the Company issued to Maruishi (refer to Note 12) 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 Preferred Stock upon the conversion of the Notes (refer to Note 8).

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As of December 31, 2013, the Company was authorized to issue up to 29,402,200 shares of convertible preferred stock, $0.001 par value per share (the Preferred Stock) (consisting of 1,677,118 shares of series A Preferred Stock 2,254,417 shares of series B Preferred Stock, 10,930,946 shares of series C Preferred Stock, 12,260,845 shares of series D Preferred Stock, 173,611 shares of Junior Preferred Stock, and 2,105,263 shares of Junior A Preferred Stock respectively). The Series A Preferred Stock, the Series B Preferred Stock, the Series C Preferred Stock and the Series D Preferred Stock are collectively referred to as the Senior Preferred Stock).

Upon the closing of the Company s IPO on February 5, 2014, all outstanding shares of the Company s Preferred Stock were automatically converted into an aggregate of 12,554,188 shares of its common stock. Refer to Note 22, Subsequent Events.

The following tables summarize the outstanding Preferred Stock as of December 31, 2011, December 31, 2012 and December 31, 2013:

As of December 31, 2011

	Preferred Shares Authorized	Preferred Shares Issued and Outstanding	Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Junior			$	$	
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
	26,462,507	26,462,507	$ 58,030	$ 58,168	11,525,313

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

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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	670,847
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	12,554,188

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 are 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 have been paid to the holders of the Preferred Stock in respect of their liquidation preferences, then the remaining assets of the Company will be 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 be up to $70,000, exclusive of any declared, but unpaid dividends.

The amount that each holder of Preferred Stock will receive upon liquidation, dissolution or winding up of the Company will be the greater of the cumulative amounts described above or the amount that such holder of Preferred

Stock would receive if the shares of Preferred Stock converted into common stock immediately prior to the liquidation, dissolution or winding up of the Company.

Since the Preferred Stock may become redeemable upon an event that is outside of the control of the Company, the Preferred Stock has been classified outside of permanent equity.

Conversion

Each holder of Preferred Stock may 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

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0.473282, respectively. The conversion ratio for all Preferred Stock is 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 shall automatically convert into common stock at the then effective applicable conversion rates for such shares. Refer to Note 22, Subsequent Events, related to such conversion in connection with the Company s initial public offering.

Dividends

Dividends on all series of outstanding Preferred Stock are 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. Through December 31, 2013, no dividends have been declared or paid by the Company.

Voting Rights

As set forth in the Company s amended and restated certificate of incorporation, the holders of Senior Preferred Stock are 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.

Registration Rights

The 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.

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11. Stockholders (Deficit) Equity

Except as described in Note 10, 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. Refer to Note 10, *Convertible Preferred Stock*, for additional information regarding the preferential rights of the preferred stockholders.

As of December 31, 2012 and December 31, 2013, the Company was authorized to issue up to 43,000,000 and 50,000,000 shares, respectively, of common stock, $0.001 par value per share.

As described in Note 2, *Summary of Significant Accounting Policies*, prior to its initial public offering, the Company utilized methodologies in accordance with the Practice Aid to support the fair value of its common stock at key points in time. In conducting these valuations, the Company considered all objective and subjective factors that it believed to be relevant for each valuation conducted, including its best estimate of its business condition, prospects and operating performance at each valuation date.

The following table summarizes common stock reserved for conversion of Preferred Stock and the exercise of warrants and options:

	Year Ended December 31,	
	2012	2013
Conversion of Series A convertible preferred	800,000	670,847
Conversion of Series B convertible preferred	948,000	901,757
Conversion of Series C convertible preferred	4,682,580	4,372,369
Conversion of Series D convertible preferred	4,154,422	4,818,216
Conversion of Junior convertible preferred	69,444	69,444
Conversion of Junior A convertible preferred		842,105
Series B and C anti-dilution shares	940,311	879,450
Exercise of warrant	19,851	19,851
Exercise of stock options	1,247,959	1,247,959
	12,862,567	13,821,998

12. Collaborations

Chong Kun Dang Pharmaceutical Corporation

In April, 2012, the Company entered into a license agreement with Chong Kun Dang Pharmaceutical Corporation (CKD) that provides CKD with the exclusive rights to develop, manufacture and commercialize products containing CR845, the Company s lead product candidate, in South Korea. Under the 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 this license 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 as 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.

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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 addition, the Company received a milestone payment of $750 during the year ended December 31, 2012 related to the Company s achievement of U.S. clinical development milestones stated in the CKD license agreement. The next potential milestone that the Company will most likely be entitled to receive under the license agreement will be a clinical development milestone for the completion of a Phase 1b clinical trial in the U.S. for a certain indication. If achieved, this milestone will result in a $250 payment being due to the Company.

During the year ended December 31, 2012, the Company recorded revenue related to the CKD license and milestones of $1,190, net of South Korean withholding tax of $206.

Maruishi Pharmaceutical Co., Ltd.

In April 2013, the Company entered into a license agreement with Maruishi under which the Company granted Maruishi an exclusive license to develop, manufacture, and commercialize products containing CR845 for acute pain and uremic pruritus in Japan. The Company and Maruishi are responsible to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845 in the United States and Japan, respectively. In addition, the Company will provide 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. The Company is also entitled to receive aggregate milestone payments of $6,000 for pre-defined clinical development events and $4,500 for regulatory events. The Company will account for any future milestone payments under ASC 605 *Revenue Recognition Milestone Method*. At the time of execution of this license 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 as they relate to clinical success and advancement within the FDA drug development platform.

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 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.

As indicated in Note 2, the Company accounts for arrangements of this type under ASC 605-25, *Multiple Deliverable Revenue Arrangement*. The Company has identified two deliverables under this guidance: (1) the license; and (2) the research and development (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

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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. 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) was allocated between the two units. The Company used its best estimate of the selling price of these units, since, as described in Note 2, 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, the management of the Company has determined that the license and the R&D services have 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 and $5,700 assigned to the R&D services. As a result, the Company recognized $9,637 of the license revenue and $2,225 of R&D service revenue during the year ended December 31, 2013. The remaining amount assigned to the R&D services has been deferred and will be recognized as the services are provided.

13. 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. The 2004 Plan provides for the issuance of 1,336,600 shares of common stock. 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. As of December 31, 2013, options to purchase 490,160 shares of common stock were granted and outstanding under the 2004 Plan.

A summary of the Company s option activity as of December 31, 2013 and changes during the year then ended is as follows:

	Number of Options	Weighted-Average Exercise Price	Aggregate Intrinsic Value
Outstanding at December 31, 2012	557,160	$ 1.28	
Granted			
Forfeited	(67,000)	(0.85)	
Exercised			
Outstanding at December 31, 2013	490,160	$ 1.34	$ 4,191

Weighted average remaining contractual life as of December 31, 2013	4.7 years		
Options exercisable at December 31, 2013	460,158	$ 1.35	$ 3,935
Weighted average remaining contractual life as of December 31, 2013	4.5 years		

The total fair value of options vested during the years ended December 31, 2011, December 31, 2012 and December 31, 2013 was $94, $65 and $75, respectively. The intrinsic value of options exercised during the years ended December 31, 2011, 2012 and 2013 was $2, $10 and $0, respectively.

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The fair values of the stock options granted were estimated using the Black-Scholes option valuation model. The risk-free rate is based on the U.S. Treasury yield curve in effect at the time of grant. The expected life of stock options granted to employees was 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 life of stock options granted to non-employees was determined using the options maximum contractual life of ten years. Expected volatility was based on an analysis of guideline companies in accordance with ASC 718.

The following ranges of assumptions were used to compute stock-based compensation:

	December 31,		
	2011	**2012**	**2013**
Risk-free interest rate	1.14% 2.3%	1.77%	2.5% 3.2%
Expected volatility	71% 72%	73%	71% 72%
Expected dividend yield	0%	0%	0%
Expected life of employee options (in years)	6.25		
Expected life of nonemployee options (in years)	3 9	2 8	1.5 7
Forfeiture rate	20%	20%	20%
Weighted-average fair value at the date of grant	$0.55		

The Company recorded compensation expense in the accompanying Statements of Operations relating to stock options issued to employees of $85, $43, and $30 for the years ended December 31, 2011, 2012 and 2013, respectively.

The Company also occasionally grants stock options to consultants. Such grants are accounted for pursuant to ASC 505, *Equity-Based Payments to Non-Employees* (refer to Note 2). The Company estimates the fair value of each option using the Black-Scholes model at issuance and then revalues the option on each reporting date until performance is complete. The total expense for the years ended December 31, 2011, 2012 and 2013 was $10, $18 and $93, respectively.

As of December 31, 2013, the total compensation expense relating to unvested options not yet recognized was $41, which is expected to be realized over a weighted average period of 1.4 years. The Company will issue shares upon exercise of options from common stock reserved.

14. Income Taxes

The Company s benefit from income taxes is as follows:

	December 31,		
	2011	2012	2013
Current:			
Federal	$	$	$
State	(35)	(31)	(30)
	(35)	(31)	(30)
Deferred:			
Federal			
State			
Benefit from income taxes	$ (35)	$ (31)	$ (30)

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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.

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

	December 31,		
	2011	2012	2013
Income taxes using U.S. federal statutory rate	34.00%	34.00%	34.00%
State income taxes, net of federal benefit	7.03%	5.60%	6.03%
Impact of R&D tax credit on effective tax rate	2.80%	0.00%	12.04%
Impact of foreign tax credit on effective tax rate	0.00%	3.27%	0.00%
Stock option shortfalls and cancellations	0.00%	(2.54%)	0.00%
Provision to return adjustments	(3.48%)	(1.95%)	(1.42%)
Change in valuation allowance	(40.00%)	(37.89%)	(49.90%)
	0.35%	0.49%	0.75%

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

	December 31,	
	2012	2013
Net operating loss carryforwards	$ 21,048	$ 21,433
Federal and state tax credits	2,419	2,947
Stock-based research and development expense	92	67
Accelerated depreciation	1,121	860
Stock-based compensation expense	48	85
Rent expense	148	136
Accrued vacation	17	32
	24,893	25,560
Valuation allowance	(24,893)	(25,560)

Net deferred tax asset	$	$

A 100% valuation allowance has been recorded on the deferred tax asset as of December 31, 2012 and 2013 because management believes it is more likely than not that the asset will not be realized. The change in the valuation allowance during 2012 and 2013 was $2,456 and $667, respectively.

The Company applies the provisions of ASC 740, *Income Taxes*, which prescribes a comprehensive model for how a company should recognize, measure, present, and disclose in its financial statements uncertain tax positions that the company has taken or expects to take on a tax return. The financial statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. As of December 31, 2012 and 2013, 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.

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At December 31, 2013, the Company had federal and state net operating loss carryforwards of approximately $55,656 and $50,701, 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 $2,311 and $651 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 2013 remain open to U.S. federal and state tax examinations.

15. License and Research Agreements

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 and recorded research and development expense of $50 during the year ended December 31, 2005 based on the aggregate fair value of the common stock as determined by the board of directors.

Upon an exit event, as defined in the Glasgow License Agreement, Glasgow has the option to require the Company to guarantee a return of $1,000 on its 200,000 shares of common stock 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 of $95 as both a long-term liability and research and development expense as of and for the year ended December 31, 2005. 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 will be 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, 2012, the estimated fair value of the liability, with consideration given to the probability of an exit event occurring, was determined to be $35. 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. The Company classifies the liability within Level 3 as the probability factor is an unobservable input and significant to the valuation model. The Company has used a probability factor of 10% in all periods from 2005 to 2013. The probability rate is 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 result in a higher liability while an increase in the stock price would reduce the liability. The decrease in the value of the liability of $25 in 2012 and $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.

16. Earnings (Loss) per Share

The Company computes basic earnings (loss) per share available to common stockholders using the two-class method, which includes the weighted-average number of common stock shares outstanding during the period and other

securities that participate in dividends (a participating security). The Company s convertible preferred stock are participating securities as defined by ASC 260-10, Earnings per Share. Under the two-class method, basic net earnings (loss) per share available to common stockholders is computed by dividing the net earnings (loss) available to common stockholders by the weighted-average number of common shares outstanding for the period. Diluted net earnings (loss) per share available to common stockholders is computed using the more dilutive of (1) the two-class method, or (2) the if-converted method. The Company allocates net earnings 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.

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

Diluted net earnings (loss) per share available to common stockholders gives effect to all potentially dilutive securities, including convertible preferred stock, convertible promissory notes and shares issuable upon the exercise of outstanding stock options and warrants, using the treasury stock method. For the years ended December 31, 2011, 2012 and 2013, the Company has excluded the effects of all potentially dilutive shares, which include convertible preferred stock, convertible promissory notes, warrants for common stock and common stock options, from the weighted-average number of common shares outstanding as their inclusion would be anti-dilutive due to the Company s net losses.

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

	Year Ended December 31,		
	2011	2012	2013
Basic:			
Weighted average shares outstanding	3,235,743	3,299,993	4,133,138
Diluted:			
Weighted average shares outstanding	3,235,743	3,299,993	4,133,138
Convertible preferred stock*			
Common stock options*			
Common stock warrants*			
Convertible promissory notes (as converted)*			
Demoninator for diluted earnings (loss) per share available to common stockholders	3,235,743	3,299,993	4,133,138

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

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

	Year Ended December 31,		
	2011	2012	2013
Net loss	$ (9,806)	$ (6,271)	$ (3,963)
Add back: extinguishment of preferred shares			891
Net loss attributable to common stockholders Basic	$ (9,806)	$ (6,271)	$ (3,072)

Net loss	$ (9,806)	$ (6,271)	$ (3,963)
Add back: extinguishment of preferred shares			891
Net loss attributable to common stockholders Diluted	$ (9,806)	$ (6,271)	$ (3,072)
Net loss per share attributable to common stockholders:			
Basic and Diluted	$ (3.03)	$ (1.90)	$ (0.74)
Weighted-average common shares outstanding attributable to common stockholders			
Basic and Diluted	3,235,743	3,299,993	4,133,138

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The following common stock equivalents were excluded from the calculations of diluted loss per share available to common stockholders because their inclusion would have been anti-dilutive.

	Year Ended December 31,		
	2011	**2012**	**2013**
Convertible preferred stock	11,525,313	11,594,757	12,554,188
Common stock options	660,701	557,160	490,160
Common stock warrants	19,851	19,851	19,851
Convertible promissory notes		702,928	

17. Related Party Transactions

The Company entered into a consulting agreement with a founder and a common stockholder of the Company to provide scientific advisory services. Total expenses under this agreement were $132, $129 and $134 for the years ended December 31, 2011, 2012 and 2013, respectively. Included in accounts payable and accrued expenses as of December 31, 2012 and, 2013 was $24 and $0, respectively, for amounts due to this stockholder.

18. 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 months of service. The plan allows the Company to match employee contributions; however, there have not been any matching contributions paid to date.

19. Commitments and Contingencies

Operating Leases

The Company leases its operating facility located in Shelton, Connecticut. The lease agreement, as amended, requires monthly lease payments through October 2017. The lease is renewable at the expiration for two successive terms of five years. 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 $1,207, $998, and $790 of unamortized incentive allowance plus $385, $379 and $349 of accrued rent at December 31, 2011, 2012 and 2013, respectively.

Total rent expense under operating leases was $640, $618 and $616 for the years ended December 31, 2011, 2012, and 2013, respectively.

Future minimum rental payments under operating leases at December 31, 2013 are as follows:

2014	$ 860
2015	886
2016	913
2017	740
	$ 3,399

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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 5).

The Company also has commitments under certain license and research agreements (refer to Note 15).

20. Legal Matters

From time to time, the Company is 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.

21. Quarterly Results of Operations (Unaudited)

The following tables contain selected financial data for each quarter of the years ended December 31, 2012 and 2013. 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, 2012 and 2013. The operating results for any period are not necessarily indicative of results for any future periods.

	Year Ended December 31, 2012			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$	$ 563	$ 627	$
Net loss available to common stockholders Basic and Diluted	(2,300)	(1,006)	(1,168)	(1,797)
Loss per share available to common stockholders Basic and Diluted	$ (0.71)	$ (0.31)	$ (0.35)	$ (0.54)

	Year Ended December 31, 2013			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenues	$	$ 9,973	$ 1,018	$ 973

Net (loss) income available to common stockholders	Basic	(1,748)	1,475	(4,575)	(2,093)
Net (loss) income available to common stockholders	Diluted	(1,748)	5,424	(4,575)	(2,093)
(Loss) income per share available to common stockholders Basic		$ (0.48)	$ 0.34	$ (1.07)	$ (0.49)
(Loss) income per share available to common stockholders Diluted		$ (0.48)	$ 0.32	$ (1.07)	$ (0.49)

The Company uses the two-class method to calculate earnings (loss) per share (refer to Note 16). During the second quarter of the year ended December 31, 2013, the Company recorded net income, although for the full year ended December 31, 2013, the Company recorded net loss. For purposes of calculating basic net income per share for the second quarter, the Company excluded from the numerator $3,869 of net income attributable to participating securities. For purposes of calculating diluted earnings per share, such amount was included in the numerator together with interest on convertible promissory notes. Common shares issuable upon exercise of outstanding stock options, assumed conversion of convertible preferred stock and convertible promissory notes were included in the denominator on an as-if converted basis.

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However, net loss for the full year ended December 31, 2013 was not allocated to preferred stockholders because they are not obligated to participate in the Company s net losses. Diluted loss per share excluded common shares issuable upon exercise of outstanding stock options, assumed conversion of convertible preferred stock and convertible promissory notes because they were anti-dilutive. Consequently, the sum of net (loss) income and net (loss) income per share for the quarters in the table above do not equal those measures for the full year ended December 31, 2013.

22. Subsequent Events

Reverse Stock Split

The Company s Board of Directors and stockholders approved a 1-for-2.5 reverse stock split of the Company s common stock effective on January 16, 2014, which resulted in an adjustment to the preferred stock conversion price to reflect a proportional decrease in the number of shares of common stock to be issued upon conversion. All share and per share amounts in the financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split.

Initial Public Offering

On January 30, 2014, the Company s registration statement on Form S-1 (File No 333-192230) was declared effective for its IPO, pursuant to which the Company registered the offering and sale of 5,750,000 shares of common stock (including 750,000 shares upon exercise of an option by the underwriters) at a public offering price of $11.00 per share for an aggregate offering price of $63,300.

As a result of the IPO, the Company received net proceeds on February 5, 2014 of approximately $55,900 from the sale of 5,750,000 shares of common stock, after deducting approximately $7,400 of underwriting discounts and commissions and estimated offering expenses payable by the Company.

Upon the closing of the Company s IPO, all outstanding shares of the Company s preferred stock were automatically converted into an aggregate of 12,554,188 shares of its common stock.

2014 Stock Incentive Plan

The Company s board of directors adopted, and its stockholders subsequently approved, its 2014 Equity Incentive Plan, or 2014 Plan, in January 2014. The 2014 Plan became effective immediately upon the signing of the underwriting agreement for the Company s initial public offering. The 2014 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights, performance stock awards and other forms of equity compensation, or collectively, stock awards. Additionally, the 2014 Plan provides for the grant of performance cash awards. Incentive stock options may be granted only to employees. All other awards may be granted to employees, including officers, non-employee directors, and consultants. No incentive stock options may be granted under the 2014 Plan after the tenth anniversary of the effective

date of the 2014 Plan.

Initially, the aggregate number of shares of the Company s common stock that may be issued pursuant to stock awards under the 2014 Plan is 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 exercise of incentive stock options under the 2014 Plan is 30,000,000 shares.

On January 30, 2014, the Company granted 387,000 stock options with an exercise price equal to the initial public offering price ($11.00) to executives and employees of the Company under the 2014 Plan.